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Association of HbA1c with Kidney Dysfunction in Diabetes Mellitus and Cardiovascular Diseases

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ABSTRACT

Diabetes mellitus (DM) and cardiovascular diseases (CVD) are some of the known conditions which predispose an individual to develop chronic kidney disease (CKD). Serum Creatinine (SCr) is the most widely used endogenous marker of GFR (Glomerular Filtration Rate), expressed as its serum concentration or renal clearance. Estimated GFR (eGFR) has been devised for more valid estimate of GFR. Association of HbA1c in renal dysfunction in DM and CVD is recently postulated. The study aimed to evaluate the association of HbA1c & eGFR in DM and CVD. Three hundred seventy subjects including 100 healthy controls, 100 diabetic patients, 100 patients with CVD and 70 patients with both DM and CVD were selected. They were analysed for SCr and HbA1c. The eGFR was calculated by four variable Modification of Diet in Renal Disease (MDRD) equation using QxMD nephrology calculator. Variation in SCr levels among the study groups as compared to controls was not statistically significant. Decrease in e-GFR and increase in HbA1c values in study groups as compared to controls was found statistically significant ($p<0.01$). Statistically significant positive correlation of HbA1c with SCr values and negative correlation of HbA1c with eGFR values is observed in Controls, DM, and DM with CVD, however, it was not statistically significant in CVD patients. Increased HbA1c in monitoring DM raises an attention for complete evaluation of Renal Function Tests. eGFR can be routinely implemented in renal function tests for early diagnosis of preventable renal impairment due to DM or CVD.

KEY WORDS: cardiovascular disease, diabetes mellitus, eGFR, HbA1c, kidney dysfunction

INTRODUCTION:

Diabetes Mellitus (DM)is one of the major risk factors for chronic kidney disease (CKD). GFR (Glomerular Filtration Rate) provides a tool for evaluation of kidney function. Decrease in GFR precedes all forms of kidney failure. Creatinine is freely filtered at the level of glomerulus and its concentration is inversely proportional to GFR. However, a small but significant and variable proportion of creatinine appearing in the urine is derived from tubular secretion. Creatinine concentration in isolation has a complicated nonlinear relationship to kidney function measured as GFR. This filtration may lead to inadequate recognition of CKD in patients with risk factors for CKD. In patients with CKD, extra renal clearance of creatinine blunts the anticipated increase in serum creatinine in response to falling GFR, at early stages of CKD (Table 1)[1].

Though specific, serum creatinine (SCr) may not exceed upper limit of reference range, until Glomerular Filtration Rate or Creatinine Clearance Rate (CCR) is reduced by 60% of normal. Commonly CCR is a more sensitive indicator of early glomerular dysfunction than that of SCr concentration [2]. Diabetic control is not reflected reliably by traditional blood glucose estimations only due to wide fluctuations. HbA1c provides average glycemia over previous 120 days[3]. Glycated hemoglobin (HbA1c) is an important indicator for long-term glucose control and has recently been recommended for use in the diagnosis of diabetes mellitus (DM) by the American Diabetes Association (ADA)[4]. However, the use of HbA1c for identifying pre-diabetics is a controversial topic[5]. In 2015, the ADA suggested that an HbA1c of 5.7–6.4% (39–46 mmol/mol) is reasonable for the diagnosis of pre-diabetes and that patients withHbA1c > 6.0% (>42 mmol/mol) should be considered to be at very high risk for DM[4]. Many studies have reported an

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association between HbA1c and Metabolic Syndrome in non-DM patients[6–8]. Both are recommended to identify early risks for renal impairment at reversible stage[9].

Estimation of GFR by using Modification of Diet in Renal Disease (MDRD) equation, which is based on SCr, age, sex, ethnicity and body size could improve the GFR prediction from SCr. The MDRD equation predicts GFR over a wide a range of values and can be used for identifying renal insufficiency, assessing progression of renal disease and detecting onset of end stage renal disease (ESRD). It does not require collection of timed urine sample, measurement of height and weight, and cause of renal disease. For early detection of CKD, evaluation of eGFR should be performed for all individuals at risk of CKD even if they show no microalbuminuria. Also, by the time microalbuminuria manifests itself almost 25% of nephron function is already lost. Early detection allows enough time for diagnosis and treatment but requires explicit testing strategies for asymptomatic individuals at risk[10,11].

This study was designed to evaluate the association of HbA1c & eGFR in Diabetes Mellitus (DM) and Cardiovascular Diseases (CVD).

MATERIALS AND METHODS:

Ethical approval for the present study was obtained from the Institutional Review Board. The study sample consisted of 370 individuals in age group 40-60 years. The study subjects comprised of 100 healthy controls, 100 pre-diagnosed patients with DM, 100 patients with CVD and 70 patients having both DM and CVD. From each study subject 5 mL of fasting venous blood was drawn by disposable syringe with full aseptic precaution. 1 mL was transferred to an Eppendorf tube with EDTA for HbA1c analysis and 4 ml of collected blood was taken in a properly cleaned & dried test tube without anticoagulant for serum creatinine.

Scr estimation was done on Olympus AU 680 Clinical Chemistry Analyzer with Modified Jaffe's Method. GFR was estimated by the 4 variables Modification of Diet in Renal Disease (MDRD) equation using QxMD nephrology calculator. Low eGFR was defined as eGFR<60 mL/min/1.73m2. MDRD Formula is given below:

eGFR = $186 \times (SCr)^{-1.154} \times (\text{Age in years})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if Black})$

HbA1c estimation was done on Chem-7 Semiautomatic analyser with Ion Exchange Resin, Binding Method. Patients were studied by categorizing them depending on HbA1c<6.5% and>6.5%. Individuals with HbA1c <6.5% were considered with good glycaemic control.

Results were expressed as Mean ± SEM. Data were analysed with SPSS Statistical Software (v22.0). Unpaired 't' test & Pearson's Correlation test were done for the comparison and correlation with each other among the study groups. $p < 0.05$ was considered as significant.

RESULTS:

The study population comprising of 370 subjects wasinvestigated for serum creatinine and HbA1c values. The eGFR was calculated using MDRD formula. Gender distribution in the study population is given in Table 1.

Table 1: Gender distribution: Study Population.

Study Groups	Males	Females
Controls	54 (54%)	46 (46%)
DM	48 (48%)	52 (52%)
CVD	49 (49%)	51 (51%)
DM + CVD	36 (51.42%)	34 (84.58%)
Total	187 (50.54%)	183 (49.46%)

Table 2 : Serum Creatinine among Study Groups.

Study Groups	Mean	SEM	p - value
Controls	1.14	0.06	
DM	1.20	0.04	0.5420
CVD	1.04	0.03	0.1271
DM + CVD	1.07	0.04	0.3384

21.9% (81/370) of the subjects had decreased eGFR (<60 ml/min/1.73 m^2) indicative of CKD. 22.22% (18/81) subjects with decreased eGFR had SCr values within the reference range (0.6-1.2 mg/dl). 77.78% (63/81) subjects with decreased eGFR, had high SCr values.

Among subjects with decreased eGFR, 50.61% were suffering from diabetes mellitus, 8.64% were suffering from CVD and 23.46% were suffering from DM as well as CVD. Frequency of decreased eGFR in diabetic subjects was 41%, in CVD subjects was 7.00%, in control subjects was 14% and that in subjects suffering from DM as well as CVD was 19%. Levels of SCr, e-GFR and HbA1c were compared among the study groups as given in Table II, III and IV respectively. Variations in SCr levels among the study

Table 3 : e-GFR among the Study Groups.

Study Groups	Mean	SEM	p - value
Controls	79.85	1.93	
DM	65.95	1.95	< 0.0001
CVD	73.81	1.12	< 0.01
DM + CVD	69.84	2.12	< 0.001

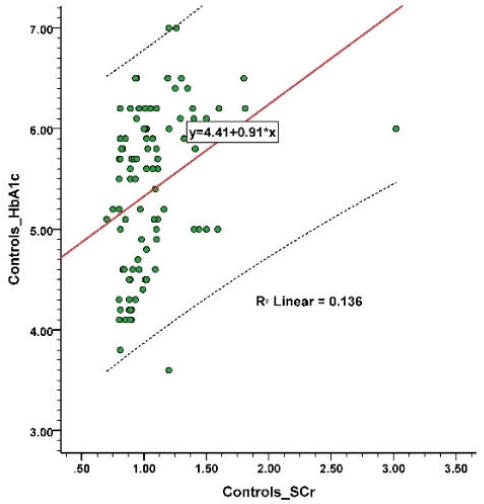

Figure 1: Correlation of SCr & HbA1c in Controls.

groups i.e. DM (n=100, p>0.05), CVD (n=100, p>0.05) and DM with CVD (n=70, p>0.05) as compared to controls (n=100) was not statistically significant (Table 2).

Decrease in e-GFR in study groups groups i.e. DM (n=100, p<0.0001), CVD (n=100, p<0.01) and DM with CVD (n=70, p<0.001) as compared to controls (n=100) was found statistically significant (Table 3). HbA1c levels in study groups i.e. DM (n=100, p<0.0001), CVD (n=100, p<0.0001) and DM with CVD (n=70, p<0.0001) compared to controls (n=100) are found to be significantly increased (Table 4).

Correlation of SCr and eGFR values with HbA1c levels among the study groups was studied with Pearson's correlation test, as given in Table 5.

Statistically significant positive correlation of HbA1c with SCr values is observed in Controls

Table 4 : HbA1c among the Study Groups.

Study Groups	Mean	SEM	p - value
Controls	5.40	0.08	
DM	8.77	0.20	< 0.0001
CVD	6.10	0.07	< 0.0001
DM + CVD	10.25	0.23	< 0.0001

Table 5: Correlation of Serum Creatinine and eGFR with HbA1c among the Study Groups,

Study Groups	Parameter	HbA1c		p - value
		r	R^2	
Controls	SCr	0.209	0.034	< 0.05
DM		0.624	0.389	< 0.001
CVD		0.001	0.000	0.991
DM + CVD		0.682	0.466	< 0.001
Controls	eGFR	-0.673	0.454	< 0.001
DM		-0.803	0.645	< 0.001
CVD		-0.052	0.003	0.304
DM + CVD		-0.932	0.869	< 0.001

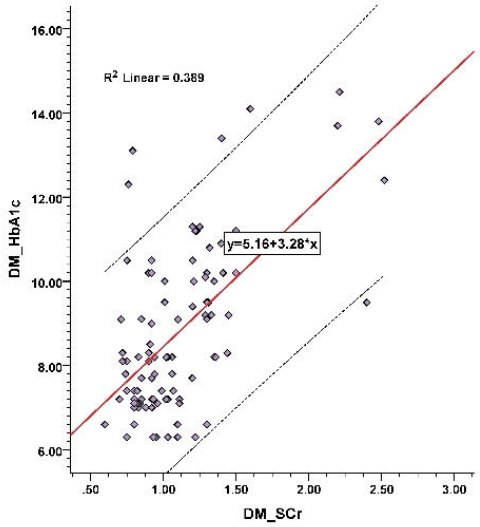

Figure 2: Correlation of SCr & HbA1c in DM patients

(n=100, p<0.05) (Figure 1), DM (n=100, p<0.001) (Figure 2), and DM with CVD (n=70, p<0.001) (Figure 3), but it was not statistically significant in CVD patients (n=100, p>0.05).

There was statistically significant negative correlation of HbA1c with eGFR values in Controls (n=100, p<0.001) (Figure 4), DM (n=100, p<0.001)(Figure 5), and DM with CVD (n=70, p<0.001) (Figure 6), but it was not statistically significant in CVD patients (n=100, p>0.05).

DISCUSSION:

Diabetic nephropathy is a chronic microvascular complication in uncontrolled DM. In early renal impairment, classical markers (Urea & Creatinine) may be normal, but there are early glomerular changes like thickening of basement membrane, accumulation of matrix material in the mesangium, subsequently nodular deposits with

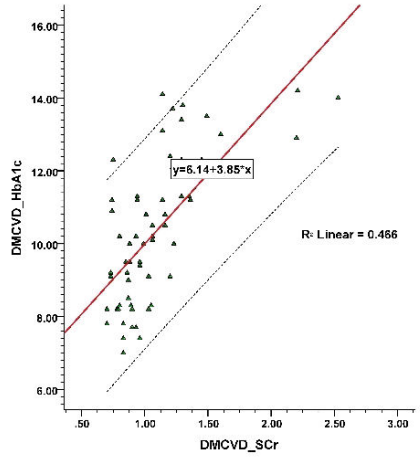

Figure 3 : Correlation of SCr & HbA1c in DM+CVD.

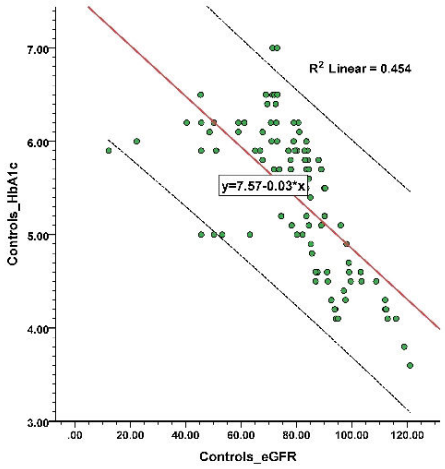

Figure 4: Correlation of eGFR & HbA1c in Controls.

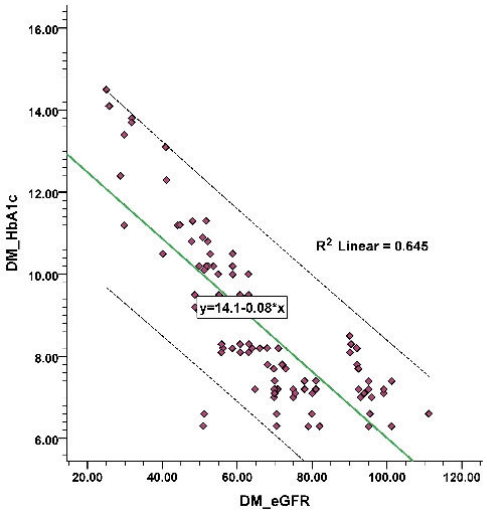

Figure 5: Correlation of eGFR & HbA1c in DM.

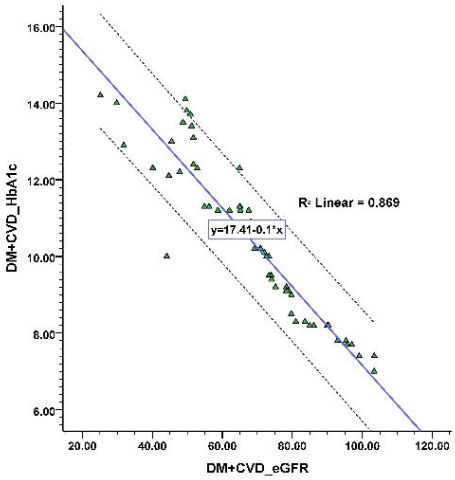

Figure 6: Correlation of eGFR & HbA1c in DM+CVD.

consequent microalbuminuria. At this stage, glomerular pathological changes can be reversed by pharmacological intervention[12]. So, newly detected or known DM patients need monitoring for glycemic control, with simultaneous monitoring for early reversible nephropathy.

100 known DM patients were taken in the study in the age group of 40-60 years. Age distribution was similar to Sheikh et al[13] & Mogensen et al[14]. In contrast to Venugopal & Lyer[15] where majority of subjects were overweight or obese, majority of subjects in our study were with normal BMI.

On comparison, the variation in mean SCr values in the study subjects compared to controls wasnot statistically significant. But the decrease in eGFR in patients of DM, CVD and DM with CVD was statistically significant as compared to controls. This clearly shows that the early onset of kidney dysfunction in DM and CVD was failed to be indicated by the changes in SCr values. But eGFR detects it at a very early stage even when SCr levels were in the normal reference range. These finding in the study were consistent with our hypothesis.

The extent of decrease in mean eGFR values in DM and DM with CVD patients was more as compared to the mean eGFR values in CVD group in our study. This may be attributed to the accelerated renal damage caused by damage to the glomerular basement membrane in diabetic nephropathy.

22.22% (18/81) subjects with decreased eGFR had serum creatinine values within the reference range (0.6-1.2 mg/dl). This observation in our study signifies the importance of eGFR in detecting renal dysfunction at the early stage even with normal SCr values. Moreover, amongst the

apparently healthy controls with no recorded disease or related symptomatology, the eGFR values were below the recommended range with normal SCr values in 14% of controls. This was the unique finding in our study insisting implementation of eGFR estimation in routine health check-ups along with SCr, so that the impending renal dysfunction can be detected even in normal individuals or pre-diabetic population.

In the present study, the rise in HbA1c levels in DM, CVD and DM with CVD was statistically significant compared to that in controls. Mean HbA1c levels in DM and DM with CVD were higher than those in CVD patients. This can be credited to the deranged glycaemic control in DM and DM related complications.

Seven percent of the controls showed higher HBA1c values more than the recommended range (>6.5%) indicating the borderline derangement of glycaemic control. Those individuals may be pre-diabetic, and have not been assessed for the same due to absence of significant symptomology. This observation was also encountered by Arnold et al[16] where they found over half of all nondiabetic participants at high risk of developing diabetes according to the ADA specifications (5.7–6.4%)[16] .This finding suggest incorporation of HbA1c in screening of individuals for risk ofdiabetes so as to capture a high proportion of high risk individuals.

In previous studies, higher HbA1c levels has found to be been associated with CKD in patients with diabetes, even in the absence of albuminuria and retinopathy[17,18]. Some studies have stated that HbA1c served as a powerful predictor of CVD and all-causemortality in their study population with and without diabetes[17,19-21].Very few studies have explored the association of HbA1c with CKDin the general population, regardless of the diabetic status[22,23].

In the present study, statistically significant positive correlation of HbA1c with SCr values is observed in Controls, DM, and DM with CVD, but it was not statistically significant in CVD patients.Sheik et al[13] found significantpositive correlation of HbA1c with SCr in diabetic patients.

There was statistically significant negative correlation of HbA1c with eGFR values in Controls, DM, and DM with CVD, but it was not statistically significant in CVD patients. It proved that HbA1c is equally effective as eGFR, in accessing the predisposition to renal dysfunction. Some studies reported that A1c is a reflection of long-term glycemic fluctuation, were found to increase the risk of chronic kidney disease in type 2 diabetic patients when eGFR decreased<60 ml/ min/1.73 m2[24-26]. In our study it is proved that, HbA1c is strongly associated with kidney dysfunction as evident by the significant decrease in eGFR and increased HbA1c levels in DM and CVD.

CONCLUSION:

It can be concluded that, raised HbA1c in monitoring Diabetes Mellitus raises an attention for complete evaluation of Renal Function Tests. For early diagnosis ofpreventable renal impairment due to DM or CVD, eGFR can be routinely implemented in renal function tests.

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Research Article

Role of Granulocyte Colony Stimulating Factor (G-Csf) in Neonatal Sepsis with Neutropenia

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ABSTRACT

Randomized controlled double blind trial was done at NICU, Department of Pediatrics, MLB Medical College, Jhansi to determine whether adjunctive therapy with G-CSF could reverse sepsis associated neonatal neutropenia and improve neonatal survival compared with conventional therapy. 52 neonates with sepsis and absolute neutrophil count(ANC)<1800/mm3. The G-CSF group (n=26) received G-CSF single daily dose of 10 mg/kg/day subcutaneously for 3 days along with conventional therapy while control group (n=26) received conventional therapy (antibiotic and supportive care) alone. Hematological parameters [ANC, total leukocyte count (TLC)] on day 0,1,3,7 & 14 of study entry, neonatal survival and duration of hospital stay were compared between two groups. Basic demographic profile among two groups were comparable. By day 3, ANC among G-CSF group was significantly higher 8292±605.21 compared to control group 1544.04±250.49(p value <0.0001). Mortality rate was significantly lower in G-CSF group than in control group 11.53% vs 46.15%. Duration of hospital stay in G-CSF group was 18.32±4.42 compared to 24.57±9.06 in control group(p value 0.0027). G-CSF can increase the neutrophil count, decrease mortality rate and reduce duration of hospital stay in critically ill septic neutropenic neonates. Further studies are required to confirm our results and establish the adjunctive therapy in neonatal sepsis.

KEY WORDS: absolute neutrophil count(ANC), granulocyte colony stimulating factor(G-CSF), neonatal sepsis, neutropenia.

INTRODUCTION:

Bacterial sepsis is one of the major causes of mortality in newborns. Bacterial sepsis occurs in 0.1 to 1% of term newborn[1] and is upto 50 times more common in extremely low birth weight infants[2]. Mortality from neonatal sepsis depends upon the virulence of the organism, the gestational age of neonate and the particular combination and severity of patient's concomitant illness[1,3].

Neutropenia is a common association of neonates with sepsis and is associated with increased risk of death[4]. Compared to adults, the unique susceptibility of neonates to sepsis associated neutropenia is due to a smaller neutrophil storage pool, reduced capacity of neutrophil to be mobilized from bone marrow and a slower regeneration of neutrophil from bone marrow[5]. In septic neonates smaller neutrophil storage pool is due to shortened neutrophil half life from 6.3 hrs to less than 4 hrs[6], a limited ability to augment production of neutrophil proliferative pool, defective production of cytokines and a rapid depletion of infant's neutrophil storage pool during bacteremia[7,8].

Immaturity of neutrophil functioning also coexist in neonates and these neonates fails to mount an adequate immune response during overwhelming bacterial sepsis.

Thus, in addition to conventional therapy for neonatal sepsis with antibiotic medications and supportive care, several new modes of immunotherapy such as granulocyte transfusion and intravenous immunoglobulin administration have been used to reduce mortality without any proven positive results[9].

Intravenous immunoglobulin failed to create a major impact in reducing sepsis related mortality and now the attention is more on the potential enhancement of phagocytic immaturity using the hematopoietic colony stimulating factor[10].

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rhG-CSF has been considered to enhance stochastic entry into granulocytic pathway, increase rapid egress of immature neutrophil into peripheral circulation[11] and also improve the killing capacity of mature neutrophils[12]. In addition in newborn with sepsis, short term therapy with G-CSF increased the neutrophil count and improved survival. G-CSF therapy in very low birth weight (VLBW) infants was demonstrated to be safe and tolerance is good. Clinical trials in neonates have been preceded by extensive in vitro and animal studies because of the concern about acute and long term toxicities of such agents in neonates[10].

Serious side effects of G-CSF application have not been reported[13,14].

MATERIALS AND METHODS:

The aim of this study was to determine whether the adjunctive therapy with (G-CSF) could reverse sepsis associated neonatal neutropenia and improve neonatal survival compared with conventional therapy.

Patient selection:

A prospective randomized controlled double blind trial was conducted in the Neonatal Intensive Care Unit (NICU) of MLB Medical College, Jhansi, UP, India from September 2012 to Aug 2013 with the approval of the Institutional ethics committee.

An informed consent had been taken from each of the participating neonate's parents. Neonates with clinical signs of sepsis associated with neutropenia, a positive sepsis screen based on absolute neutrophil count (ANC), Total Leukocyte count, immature to total neutrophil ratio, micro-ESR, C-reactive protein (CRP)[15] and confirmed by at least one positive blood culture in 1st 28 days of life were included in the study.

Neutropenia was defined as absolute neutrophil count <1800 cells/mm3 with minor modification of criteria of Manroe et al[16] and Mouzinho et al[17].

Inclusion Criteria:

I) Neonates of age <28 days.
II) Newborns with clinical criteria recommended by National Neonatology Forum for sepsis.
III) Absolute neutrophil count (ANC) <1800 cells/mm3.
IV) Any one of the following hematological parameter.
   a. Total leucocyte count <5000cells/mm3
   b. I/T ratio >0.2
   c. C-reactive protein (CRP) > 1mg/dl
   d. Micro ESR – increased >15mmHg on 1st hr

Diagnosis was confirmed by blood culture by Bactec method.

Exclusion Criteria:

The neonates with the following anomalies were not included in the study :-

- Major congenital anomalies
- Cyanotic congenital heart disease
- Stigma of intrauterine infection
- Intraventricular hemorrhage grade III and IV
- Inborn errors of metabolism

Treatment protocol:

Included infants were randomized to receive either (G-CSF) or conventional therapy using a randomly generated (computer generated) predetermined schedule. Investigator were divided in two teams- blinded and unblinded. Those collecting data and following babies in study group were blinded. A computer generated random number table was followed and an allocation number was assigned to each random number. Corresponding allocation numbers were also present concealed in the cover of each medication, which was not accessible to blinded team. The unblinded team administered the medication following randomization.

Prior to study, maternal characteristics, approximate gestational age, anthropometry, vitals of newborn, serum biochemistry, CRP, blood sugar and electrolytes were recorded. Gestational age was confirmed by New Ballard Score.

Both the G-CSF group and control group were treated with appropriate conventional therapeutic interventions including antibiotics, oxygen, intravenous fluid, vasopressor drugs (dopamine or dobutamine) and other standard interventions deemed necessary for the clinical treatment of neonate independent of study drug usages. Antibiotic regimens were modified subsequently according to blood culture report and sensitivity pattern.

In addition, neonates in study group received G-CSF (filgramstin) at a single daily dose of drug 10mg/kg/day for 3 days subcutaneously diluted in 5% dextrose with dilution not less than 5mg/ml[18,19].

Included infants showed no signs of disturbance in respiration, heart rate or blood pressure during administration of study medicine. Routine examinations were performed daily and vitals and all systems were closely monitored until discharge.

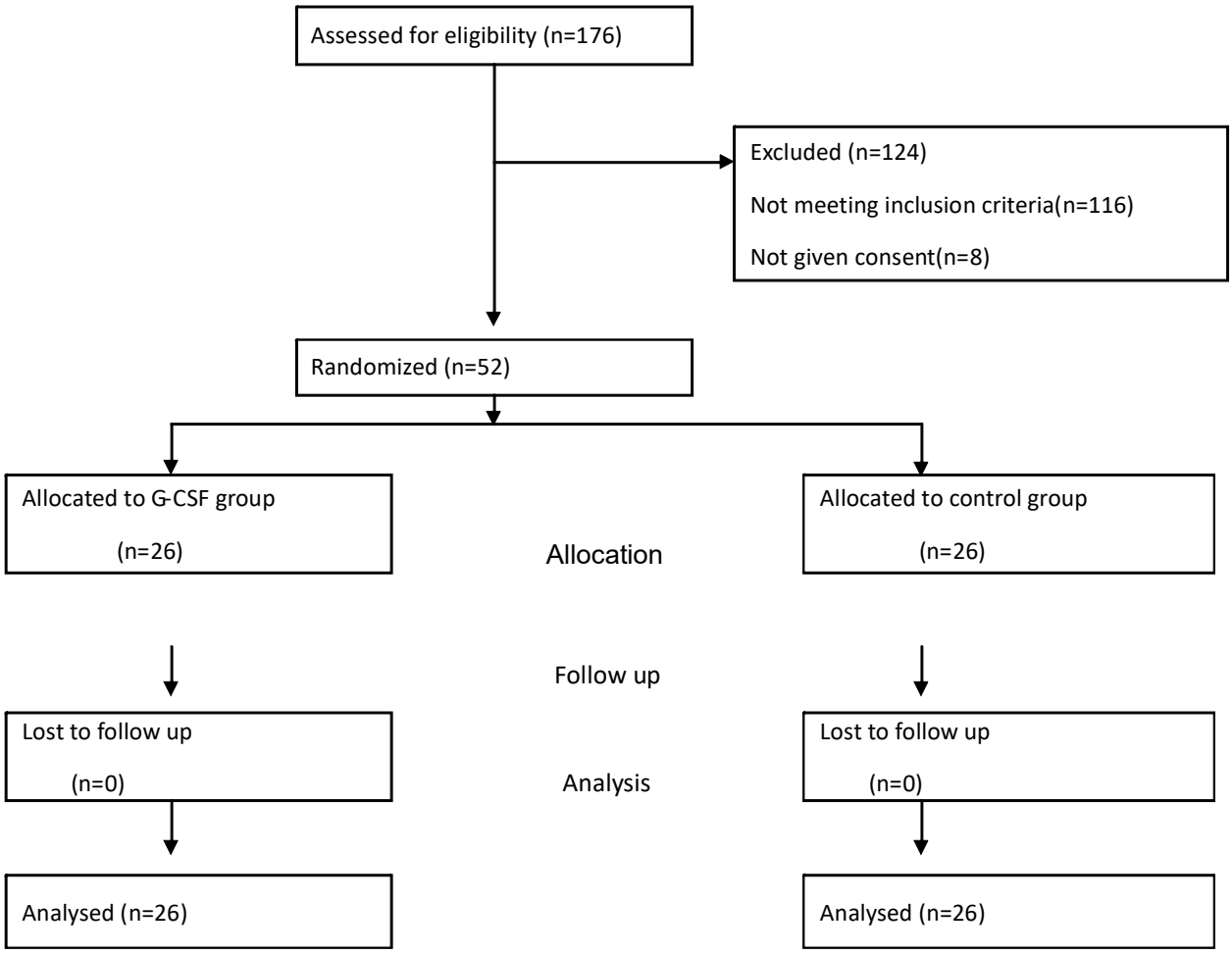

Figure 1: Flow chart for randomization and follow up.

Complete blood counts were obtained by counter autoanalyzer machine at study entry and after treatment on day 1, 3, 7 and 14. Absolute neutrophil count was obtained by manual counting from peripheral blood smear.

Statistical Analysis*:*

Data were expressed as numbers (%), and mean± SD. p value <0.05 was taken as significant. Fisher's exact t-test & Chisquare test used for comparing the two groups in regard to get significance.

RESULTS:

A total of 52 neonates with sepsis and absolute neutrophill count (ANC) <1800cells/mm3 were enrolled and randomized to receive either G-CSF (n=26) plus conventional therapy or conventional therapy (n=26) alone. All babies completed the study. The demographic clinical characteristics of both groups showed no significant difference.

Clinical hospital course:

All neonates tolerated G-CSF well and in each case no adverse reactions were identified with regard to cardiovascular performance, electrolyte balance, skin reactions, irritability or worsening of respiratory function. Patients in both the groups received conventional neonatal intensive care unit treatment for severe sepsis which included antibiotics for 10 days or more, oxygen inhalation, vasopressors and blood transfusions as and when required.

Hematological Indices

Absolute neutrophill count (ANC):

At study entry the ANC in the G-CSF group was 1479.2±269.85 compared to 1483.3±242.54 in other group which was statistically nonsignificant (p=NS).

By day 1 (After 24 hrs) of starting intervention, the G-CSF group had significantly

Table 1: Demographic characteristics of study patients.

S.No.	Variable	GCSF group (n=26) (%)	Control group (n -25) (%)	p value
1)	Birth weight (mean ±SD)	1411.15 ±204.01	1500.38 ±306.35	0.2222 (ns)
2)	Gestational age (mean ±SD) weeks	31.15 ±1.95	31±1.87	0.7734 (ns)
3)	Gender			
	Male	17 (65.38%)	18 (69.23%)	>0.05 (ns)
	Female	9 (34.62%)	8 (30.77%)	>0.05 (ns)
4)	Intrauterine growth retardation	6 (23.08%)	5 (19.23%)	>0.05 (ns)
5)	Number with			
	Early sepsis	24 (92.3%)	25 (96.15%)	>0.05 (ns)
	Late sepsis	2 (7.7%)	1 (3.85%)	>0.05 (ns)
6)	Maternal characteristics			
a)	Received antenatal care	10 (38.46%)	11 (42.31%)	>0.05 (ns)
b)	H/o premature rupture of membrane	7 (26.92%)	6 (23.08%)	>0.05 (ns)
c)	Cesarean delivery	12 (46.15%)	13 (50.0%)	>0.05 (ns)
d)	Twin pregnancy	4 (15.38%)	4 (15.38%)	>0.05 (ns)
e)	Pregnancy induced hypertension	4 (15.5%)	3 (11.5%)	>0.05 (ns)
7)	Bacteria of sepsis			
	E.Coli	10 (38.46%)	10 (38.46%)	>0.05 (ns)
	Klebsiella	10 (38.46%)	12 (46.15%)	>0.05 (ns)
	Enterobactor	2 (7.7%)	1 (3.85%)	>0.05 (ns)
	Candida	4 (15.38%)	3 (11.54%)	>0.05 (ns)

compared to the control group. ANC in G-CSF group was 4817.92±575.06 as compared to 1551.65±251.22 in control group with p value <0.0001 (Hs). Also in G-CSF group, ANC at day 1 increased by 3 fold as compared to day 0 (4817.92±575.06 vs 1479.20±269.86) which is highly significant with p value <0.0001 (HS) while in control group no significant increase in ANC at day 1 as compared to day 0(1551.65±251.22 vs 1489.38±242.54) with p value 0.3676 (ns).

By day 3, the G-CSF group had ANC of 8292±605.21 as compared to 1544.03±250.49 in the control group with a p value <0..0001 (HS). Also in G-CSF group ANC increased by 5 fold as compared to day 0 [8292.00±605.21 vs 1479.20±269.86, p value <0.0001 (HS)] while in control group 2 fold increase [2544.03±250.49 vs 1489.38±242.54, with p value 0.4279 (ns)] occured.

By day 7 the G-CSF group had ANC of 9281.82±437.27 as compared to 5223.52±369.09 in control group [p value <0.0001 (HS)]. Also there was 7 fold vs 4 fold increase in ANC compared to respective day 0 with p value in both group <0.0001 (HS).

The timing of changes in the ANC in the G-CSF group occurs sooner and remains longer than in conventionally treated group.

Mortality:

There were 11.53% (3/26) deaths in the G-CSF group as compared to 46.15% (12/26) in the control group which was significantly low (p value 0.014)

Causes of death among both groups were septic shock, DIC, and respiratory failure.

Table 2: Absolute neutrophil count.

	Day 0	Day 1	Day 3	Day 7
G-CSF group (n=26)	1479.2 ± 269.8592	4817.92 ± 575.0616	8292 ± 605.2118	9281.826 ± 437.2726
Control group(n=26)	1489.385 ± 242.5417	1551.654 ± 251.2256	2544.038 ± 250.494	5223.52 ± 369.0955
t-value	0.14313	26.53962	44.4463	36.16316
p-value	0.8868 (ns)	<0.0001 (HS)	<0.0001 (HS)	<0.0001 (HS)

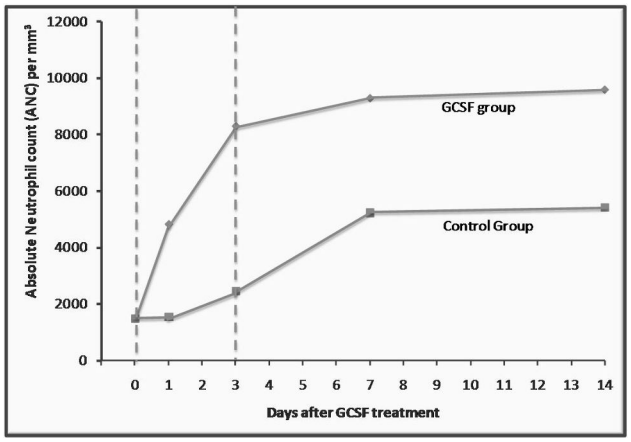

Figure 2: The timing of changes in the ANC in the G-CSF group occurs sooner and remains longer than in conventionally treated group.

Duration of hospital stay:

Duration of hospital stay in G-CSF group was 18.32±4.42 days as compared to 24.57±9.06 days in control group which was significantly low with p value 0.0027 (s).

DISCUSSION:

Our study demonstrated that preterm babies with sepsis and neutropenia who were treated with G-CSF for 3 day along with conventional care had a significantly lower mortality than the control group.

G-CSF increased the ANC and the increase in ANC in the G-CSF treated group was statistically significantly higher at day 1 than that the conventionally treated control group in which the increase only achieved significance at 7 days after entry. The neonatal response followed a predictable pattern of timing similar to observations made in adult patients in sepsis and pneumonia[20].

Overall, favorable prognosis in neonatal septicemia depends on effective host mechanism which again depends on normal hematological indices[21]. Neutropenia, when associated with neonatal sepsis, worsens the prognosis[22]. An immaturity in the quantitative and qualitative aspects of phagocytic immunity contributes to a state of relative immunodeficiency in newborn infants. GCSF is a physiological regulator of myelopoiesis and an activator of mature effective neutrophil function. It supports the clonal growth of neutrophil progenitors, primes neutrophils to increased expression of chemotactic receptors, and enhances antibody dependent cellular cytotoxicity[23]. Compared to adults, newborns do not seem to generate GCSF effectively. Estimates suggest that when sepsis is associated with severe neutropenia, mortality exceeds 50%. Relative neutropenia, though, is a low-risk group in developed countries; in developing countries with resource-limited settings, sepsis-related neonatal neutropenia is a significant cause of neonatal mortality and morbidity[24]. In addition, in developing countries, the microbiological organisms causing septicemia are different from those in developed nations; in developing countries organisms are mostly gram negative such as Klebsiella and Pseudomonas, E.coli[25].

There have been studies on the use of GCSF both as an adjunctive to treatment in neutropenic septicemic neonates and also its prophylactic use in preterm neonates, but all these studies are heterogeneous with regard to patient selection, duration of intervention, dosage and route of intervention, and outcome criteria. Duration of intervention varies widely in studies, mostly between 5 and 7 days.

It was chosen in the present study to discontinue the G-CSF therapy after 3 daily doses because the magnitude of the ANC response begins to plateau in adults after 4 days of treatment and we found that neonatal cell count had entered into normal range by then, thereby reducing cost of treatment and any possibility of side effect.

We have utilized the subcutaneous route for drug administration instead of continuous intravenous infusion as used in previous studies for which special infusion sets are needed thereby reducing cost of treatment and maintaining proper dilution of drug, and can be easily administered.

G-CSF receptors are expressed on variety of hematopoietic cells including neutrophils, monocytes, lymphocytes, platelets, leukemic cells and nonhematopoietic cells like endothelial cells, neurons and glial cells. So we also examined the effect of G-CSF on other leukocytes like lymphocytes and monocytes and found that there was no statistically significant effect on these cells.

Among the different studies, most are with positive outcomes[18,21]. Our study showed remarkable results both in terms of mortality and duration of NICU stay with the use of GCSF. So, further studies are required to confirm our results and establish this adjunctive therapy in neonatal sepsis.

CONCLUSIONS:

Neutropenia increases risk of death in neonatal sepsis and G-CSF may be used as adjunctive therapy. G-CSF improves survival and reduces duration of hospital stay when used as adjunctive therapy.

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Misplaced IUCD: Challenges and Management

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Research Article

ABSTRACT

PPIUCD programme was started in March 2011 in Kumaon region as a highly effective, non-hormonal method of contraception that can be safely used by all women regardless of breastfeeding status during this interval.There were 4481 postpartum cu-T inserted in entire Kumaon region since the programme started. This in turn has come with an increase in the number of related problems like misplaced Cu-T. The case series of 36 cases with lost strings of IUCD reported during October 2013 to January 2016 is presented herein, wherein the routine procedure of IUCD retrieval failed and were referred to our hospital for further management. 30 patients had cu-T in uterine cavity, which were successfully removed by hysteroscopy in 22 cases. It was found in pelvic cavity in 2 cases, subsequently removed by laparoscopy. Out of 36 patients, IUCD was inserted following vaginal delivery in 11 patients. 20 were previous 1LSCS, 3 were previous 2LSCS and 2 patients with Cu-T in pelvic cavity had interval Cu-T insertion. Hysteroscopy is the preferred method in management of misplaced IUCD.

KEY WORDS: hysteroscopy, laparoscopy, misplaced cu-T, PPIUCD programme.

INTRODUCTION:

Among the options available, the multi-year cost of the Copper T380A IUD makes it one of the most cost-effective contraceptive options available. According to the World Health Organization Medical Eligibility Criteria, an IUCD can be inserted in the 48 hours postpartum, referred to here as a postpartum IUCD (PPIUCD), or after four weeks following a birth.With increased use of intra-uterine devices (IUDs) for contraception, an increase in the number of related problems are reported. A frequent clinical problem is the loss of filament at the external cervical os, the 'lost tail'. The disappearance of the string or marker heralds potential problems such as retracted or torn off tail, misplacement within the cavity, intra-mural penetration or extra-uterine location. IUDs may be misplaced in as many as 5% of cases. Procedures for retrieval of a misplaced device includeextraction with a metal hook, artery forceps, thread retriever or dilatation and curettage. However, success is not ensured with above methods; failure and uterine trauma may occur. Hysteroscopy as a diagnostic and operative technique has enabled safe retrieval of misplaced IUDs. The study was planned to analyze the etiology and management of cases with misplaced or translocated intrauterine devices (IUDs) into the abdomen or into the wall of the uterus.

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MATERIALS AND METHODS:

This study was a retrospective analysis of patients records at Dr. Susheela Tiwari Hospital, Haldwani during the period October 2013–January 2016,which required an admission to the hospital for the removal of an IUD that had misplaced within the cavity or had translocated to the outside of the uterus.We present 36 cases with 'lost IUDs' in whom the routine procedure of IUCD retrieval failed and were referred to our hospital for further management. A proforma was designed containing information regarding patient's age, parity, mode and time of insertion, time duration of IUCD, mode of IUCD retrieval and its location. The collected data was analysed and compared with other studies. Presence of anIUD was confirmed either by ultrasound or X-ray.A 10 mm operative hysteroscope with grasping forceps was used for extraction of the IUD under Total Intravenous Anesthesia (TIVA).

All women whose IUC string could not be visualized at the external os of the cervix at any given

follow-up visit, even after attempting a standard maneuver of sweeping the strings from the cervical canal or trying to visualize the strings in the cervical canal using colposcopy were included in the study. All women who had voluntarily gone for IUCD removal or have seen IUD expelled out spontaneously were excluded from the study.

RESULTS:

Mean age of the patients varied from 20-40 years with maximum duration of use between 1- 2 years. Maximum cases were seen between 3-4 parity. One case of nulliparous women with history of infertility with IUCD insertion (Cu- T 380-A) inserted at peripheral hospital by an auxiliary nurse midwife on day-5 was identified. Out of 36 patients, (a) IUCD was inserted following vaginal delivery in 10 patients, (b) 20 were previous 1 LSCS, (c) 3 were previous 2 LSCS and (d) 3 patients with cu-T in pelvic cavity had interval cu-T insertion.

Maximum number of patients had time interval of 18-24 months between insertion and removal of cu-T. After confirmation of the diagnosis, out of 36 women, it was found to have expelled completely in 4 patient and it was found in cervical canal in 7 patients. IUCD was found embedded in the myometrium . In 22 women, while it was found in pelvic cavity in 3 patients.

IUCD in cervical canal was removed with the help of long artery forceps. IUCD found embedded in the myometrium was removed with the help of hysteroscope, while that in pelvic cavity was successfully removed by laparoscopy. In one patient, IUD was translocated outside the uterine cavity embedded into the omentum just behind the uterus, while it was found on the surface of the bladder in 2nd Case. In both cases, no IUD was visible on hysteroscopy despite the X-ray abdomen erect view showing IUCD in peritoneal cavity. Laparoscopy failed to visualize cu-T in one nulliparous case with cu-T in pelvic cavity. Laparotomy was done and cu-T was found bridging the two loops of large intestine. Removal of cu-T with primary repair of colonic perforation was done.

Table 1: Age of patients.

Age (year)	Number	Percentage
20-30	9	25
31-40	20	55
>40	7	20

Table 2: Parity of patients.

Parity	Number	Percentage
Nulliparous	1	2
1-2	10	28
3-4	19	53
>4	6	17

Table 3: Mode and time of insertion.

Mode and time of insertion	No. patient	Percentage
After vaginal delivery	10	28
After 1st LSCS	20	55
After 2nd LSCS	3	9
Interval IUCD insertion	3	8

Table 4: Time interval between time of insertion and removal of Cu-T.

Time interval between time of insertion and removal	No. patient	Percentage
<6 months	2	5
6-12 months	5	14
12-18 months	9	25
18-24 months	14	39
>24 months	6	17

Table 5: Location of Cu-T device.

Location of device	No. patient	Percentage
1) Intra-uterine	29	81
(a) Partially embedded in the cavity	22	61
(b) In the cervical canal	7	20
2) Extra -uterine	3	9

Table 6: Method of removal.

Removal	No. of patients	Percentage
With artery forcep	7	20
Hysteroscopic removal	22	61
Laparoscopic removal	2	6
Laparotomy	1	2

Table 7: Position and characteristics of IUDs on hysteroscopy.

Hysteroscopic findings	No. of Patients
Cu T in normal position	14
Cu T lying transversely	2
Transverse limb of Cu T in anteroposterior diameter	2
Submucosal Fibroid below Cu T	4
IUD not visualized	2

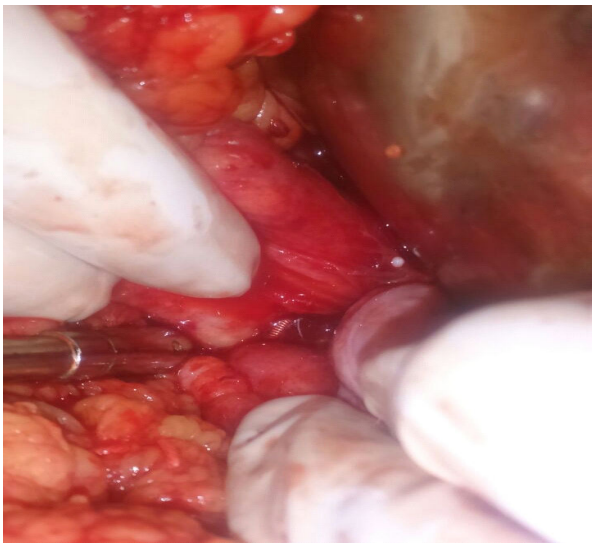

Figure 1: Cu-T bridging two large bowel loops in case of nulliparous woman removed by laparotomy.

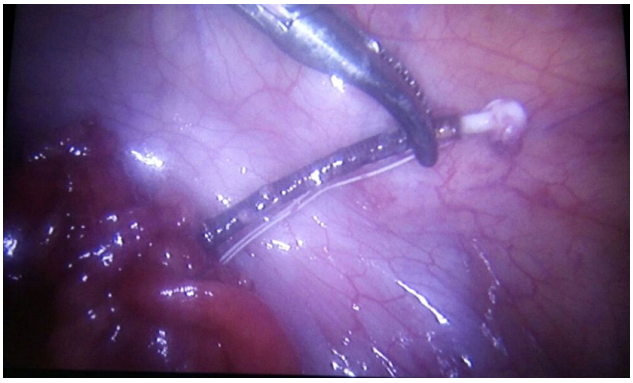

Figure 2: Cu-T outside the uterine cavity embedded in the omentum , removed laparoscopically.

DISCUSSION:

Intrauterine device is a widely used reversible method of Contraception, preferred due to long duration of birth control effect and ease of use. However it also has some serious complications such as perforation of the uterus and its migration to the abdominopelvic structures[1]. Primary perforation may occur during insertion by mechanical forces. Some of the known risk factors for IUD perforation are inadequate training of family planning providers, insertion at early puerperal period when uterus is soft and bulky, past history of perforation (formation of a new canal with previous inappropriate insertion), and anatomically highly (ante or retro) flexed uterus.

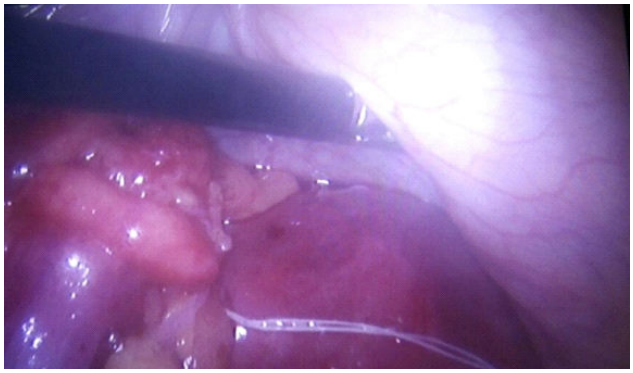

Figure3: Cu-T outside the uterine cavity embedded in the omentum , removed laparoscopically

Most of the patients were > 30 years and were grand multipara with maximum incidence following previous1LSCS.These findings are consistent with other studies [7,8]. IUCD was in the uterine cavity in 29(81%) patients. Seven (20 %) patients among those needed long artery forcep. IUCDs were adherent to uterine wall in 22 (61%) patients requiring hysteroscopic guided removal. According to Barsaul M[9] and Lawal[7], 79.79% and 63.48% patients respectively had their device inside the uterine cavity. In a study by Trivedi SS et al [10] on 38 patients with intra-uterine devices with lost strings, hysteroscopic aid was required after routine retrieval procedures failed. Thirty five intra-uterine devices could be removed easily with hysteroscope. Laparotomy was required in only one patient, for an extra-uterine Copper-T. In one series of 324 cases with misplaced IUCD one[9] in: 258 (79.93%) cases Copper-T was found in the uterine cavity and in 47 cases (14.51%) it was removed from cervical canal. In only 18 cases (5.56%), it was translocated. The incidence of uterine perforation is very low, but in the literature nearly 100 cases are reported about the extra uterine localization of IUCD.

Three patients (8%) had complete uterine perforation and transmigration to peritoneal cavity. Successful laparascopic removal was don in 02(66.6%) patients, while in the third patient, a nulliparous woman having history of Cu-T 380A insertion at peripheral hospital by an auxiliary nurse

midwife on day-5, the device was found perforating the large bowel. It was removed followed by gut repair. These findings show an increase rate of transperitoneal migration of IUCDs in this study, which reflects an improper training of medical personnel involved in the insertion of IUCD. Elahi N[8]reported 28.57 % cases, while Barsaul M et al[9] reported only 5.56 % cases of IUCD migration to peritoneal cavity.

The symptoms of an IUD perforation are diverse varyingfrom a subsequent unwanted pregnancy[2] to irritant lower urinary tract symptoms[3], chronic pelvic pain, peritonitis, and fistulae or abscess formation depending on the organ of penetration and the interval since penetration and patient's response. Ultrasonography and plain X-ray are diagnostic for echogenic and radio opaque foreign body, respectively.

World Health Organization has recommended removal of a dislocated IUD as soon as possible irrespective of their type and location[4]. It is advised to retrieve a migrated IUD by minimally invasive techniques[5]. Endoscopic techniques such as colonoscopy, hysteroscopy, and cystoscopy can be used for diagnosis and treatment depending on the location of IUD.

A review of surgical techniques to remove IUD revealed that 93% of the reported cases in literature attempted laparoscopically, but cases of both abdominal and pelvic organ perforations have the laparotomy rate of 57.1%[6]. Valle and Freeman1 advocated hysteroscopy as a primary method for locating and removing IUDs with missing tails in order to avoid unnecessary X-ray exposure and injuries by blind exploration.

CONCLUSION:

Awareness of people about this safe, valuable and reversible method of contraception, its easy availability and the provision of trained personnel for its insertion as well as a regular follow up is needed in developing countries.

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Research Article

Maternal Risk Factors of Caesarean Delivery in a Tertiary Care Hospital in Central India: A Case Control Study

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ABSTRACT

One of the most alarming features of modern obstetrics is the relentless increase in c-section rates. Medical, institutional, legal, psychological and socio-demographic factors play a contributing role. Although c-sections can be life-saving, c-section rates above the WHO recommended 15% raises global concern.India is also not excluded from this trend. It is time to realize that c-sections not only put both the mother and child at risk, but also pose huge economic burden compared to normal vaginal delivery. This study was designed to identify the maternal risk factors associated with c-sections. A hospital based case control design was approached. 360 mothers, all consenting 180 consecutive mothers who had c-section in singleton pregnancies and 180 mothers with singleton spontaneous vaginal deliveries were selected from postnatal ward. Data was collected using a pre-tested questionnaire. Out of the 11 variables examined, 7 were found statistically significant. Mothers who had a previous c-section, pre/post term pregnancy and BMI >23 kg/m2 had the highest significant proportion rates. Univariate analysis for risk calculation was done by odds ratio and their 95% Confidence Intervals was done by using Epi Info software. Analyses have revealed several important associations between maternal risk factors and c-section. Most of these factors are modifiable, and if targeted early can reduce the chances of c-section significantly.

KEY WORDS: caesarean, c-section, case control, socioeconomic status, risk factors

INTRODUCTION:

The last couple of decades saw dramatic changes in the realm of maternal and child health. Advances in modern obstetrics helped achieve better pregnancy outcomes both for the mother and child and caesarean sections played a substantial role in this regard. Recent trends show a global phenomenon of increasing rates of c-section.[1] Medical, Institutional, legal, psychological and socio-demographic factors play a contributing role. Although cesarean delivery can be life-saving, the rapid rise in c-section rates above the WHO recommended 15% raises global concern.[2]India is also not excluded from this trend. Two population based cross-sectional studies showed, a c-section rate of 32.6% from Madras city[3] and 34.4% from the city of Nagpur.[4]

The article, published online January 12, 2010 in The Lancet, reports the third phase of the WHO global survey, which was conducted in 9 Asian countries in 2007 and 2008: revealed that women who had a caesarean section without a medical need to were at least ten times more likely to be admitted to intensive care than those who gave birth normally. Where labour had already started, women who had a surgical delivery despite not requiring one were 67 times more likely to be admitted to intensive care than those who had a straightforward natural birth. Lumbiganon and associates maintain that "the most important finding of the survey is the increased risk of maternal mortality and severe morbidity in women who undergo cesarean section with no indication."[5]

There is considerable interest in determining the driving forces behind the global rise in Caesarean section rates. This attention is intensified by a widespread desire to halt and reverse this trend. To achieve this, a detailed understanding of the factors contributing to the increase is required, which may

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also help to explain the variations observed across units. Many purely obstetric factors have of course affected caesarean section rates. Along with obstetric factors, numerous characteristics of individual women like history of previous c-section, parity, height of the mother, maternal age, associated co-morbid conditions (diabetes, hypertension), demography, education and income are just a few of the factors that have been cited in the literature as being associated with Caesarean section. [1,3,4]

If these factors can be clarified, it may indicate key areas that could be targeted to control caesarean section rates. It is time to realize that c-sections not only put both the mother and child at risk, but also pose huge economic burden compared to normal vaginal delivery. With this background, this study was designed to identify the maternal medical and socio-demographic risk factors associated with c-sections.

MATERIALS AND METHODS:

A hospital based case control design was approached. (a) to identify medical and socio-demographic risk factors associated with Caesarean sections; (b) to find the association and calculate Odds ratios of these factors with Caesarean sections. The study was conducted in Obstetrics and Gynecology ward of a tertiary care hospital at NKPSIMS & RC in Nagpur, India from Feb 2014 to July 2014.

The sample size was calculated with the following assumptions, Type 1 error 5%, power of study 80%, prevalence of obesity (a risk factor) among control 17%, ratio of the case and control 1:1 and estimated odds ratio (OR) for obesity was 2.11 Estimated sample size was 177 cases (rounded to 180) for uncorrected Chi-square test and equal numbers of controls. After determining the total sample size of 360 mothers, all consenting 180 consecutive mothers who had cesarean section (cases) and 180 mothers with vaginal deliveries (control) were selected from postnatal ward. Only singleton deliveries were included in the study, mothers with twin and multiple pregnancies were excluded.

Data was collected using a pre-tested questionnaire including maternal and socio-demographic variables: age, education, residence, occupation, income, parity, number of previous cesarean sections, infertility treatment, gestational age at labor, Presence of co-morbid medical illness like diabetes mellitus and hypertension, body mass index (BMI as per proposed criteria for Asian population adopted from the Lancet)[6] and Socio Economic Status as per Modified Prasad's scale for the year 2014[7].

STATISTICAL ANALYSIS:

Data analysis was done by using Epi info software. A Chi square test was used to determine the association of various risk factors with the type of delivery. Univariate analysis for risk calculation was done by odds ratio and their 95% Confidence Intervals.

RESULTS:

The sample comprised of a total of 360 mothers with equally distributed caesarean section in singleton pregnancies (180 cases) and singleton spontaneous vaginal deliveries (180 controls). Majority of the mothers (70%) were from rural area.

Table 1 presents the proportion of mothers reporting caesarean section and non-caesarean delivery by patient characteristics and their significance level. Out of the 11 variables examined, 7 were statistically significant. Mothers who had a previous c-section ($p<0.0000001$), pre/post term pregnancy ($p=0.00012$) and BMI >23 kg/m2 ($p=0.000349$) had the highest significant proportion rates. In addition, height of the mother (<145 cm) and occupation of the mother were found to be statistically significant ($p<0.01$). The same pattern was observed with the birth order. C-section deliveries were found to be less frequent in rural area (48.2%) as compared to urban areas (54.2%).

Mothers who underwent a previous c-section were 14 times more likely to deliver again by c-section than mothers who dint have that history (OR, 14.65; 95% CI 6.49, 33.06). 59.2% of cases had a previous c-section compared to 4.04% of the controls. It was found that mothers who delivered pre or post term tend to have higher risk of c-section than those who delivered at term (OR, 2.69; 95% CI 1.56, 4.65). (preterm <37weeks of gestation; post term >42weeks of gestation)

BMI >23 kg/m2 was reported in 60.71% of the mothers who delivered by c-section compared to 23.82% of spontaneous vaginal deliveries, with an estimated OR = 2.60; 95% CI 1.61, 4.21. Similarly, 42.85% of mothers who underwent c-section were observed to be short statured (height <145 cm) compared to 20.80% of mothers who delivered normally (OR, 2.06; 95% CI 1.25, 3.40) Our study shows that a primigravid mother is 1.5 times more likely to undergo c-section compared to a multigravida (OR=1.59; 95% CI 1.04, 2.43).

Occupations other than housewives were

Table 1: Association of various socio-demographic and maternal variables with type of delivery

Variables	Caesarean	Vaginal	OR (95%CI)
Age at delivery (yrs) <20 or >30	73(56.2)	57(43.8)	1.47 (0.95-2.26)
20 – 29	107(46.5)	123(53.5)	
Literacy of mother			
>12th std	100(54.3)	84(45.7)	1.42 (0.94-2.16)
Up to 12th std	80(45.5)	96(54.5)	
Occupation of mother			
Working	69	48	1.70 (1.09-2.67)*
House wife	111	132	
Birth order			
1	82	62	1.59 (1.04-2.43)*
2 or more	98	118	
Previous CS			
Yes	67	07	14.65 (6.49-33.06)*
No	113	173	
Pregnancy duration			
Pre/post term	51	23	2.69 (1.56-4.65)*
Term	129	157	
Socioeconomic status			
Class I,II and III	75	66	1.23 (0.80-1.88)
Class IV and V	105	114	
Place of residence			
Urban	58	49	1.27 (0.80 -2.05)
Rural	122	131	
Co morbid Condition			
Present	42	23	2.07 (1.19-3.62)*
Absent	138	157	
BMI			
More than 23 Kg/m2	68	34	2.60 (1.61-4.21)*
Up to 23 Kg/m2	112	146	
Height of mother			
<145cm	54	31	2.05 (1.24 – 3.42)*
>145cm	126	149	

CI=Confidence Interval *Significant $p < 0.05$

observed in 62.16% of the cases compares to 36.36% of controls with an estimated OR, 1.709; 95% CI 1.094, 2.672. Socio-economic status (Prasad's Scale) was not found to be a risk factor with 71.4% of cases and 57.9% of controls falling either in upper or middle class (OR, 1.23; 95% CI 0.80, 2.05)

Likewise, place of residence could not be established as a risk factor with 47.54% of mothers who delivered by c-section and 42.98% of normally delivered mothers reside in urban region (OR, 1.27; 95% CI 0.80, 2.05)

Comorbidities (hypertension, diabetes; both gestational and pre-existing) were seen in 30.43% of cases compared to 14.64% of controls with an estimated OR, 2.07; 95% CI 1.19, 3.62. This study failed to identify maternal age and literacy as risk factors for c-section.

DISCUSSION:

The study examined the maternal, socio-demographic and other relevant determinants of c-section in a tertiary care teaching hospital in central India.

A highly significant association was found between caesarean deliveries and previous c-section. This observation is consistent with the findings of many other studies.[3,8-13] Leone T and associate's study conducted in six developing countries revealed that previous c-section delivery was the highest risk factor for subsequent caesarean.[11] Other studies done in developing countries like Pakistan,[8] Jamaica[9] and Oman[13] have also found that there is a strong association between previous c-section and a repeat caesarean. Mothers with a previous history of caesarean section were at an increased risk of uterine rupture and bleeding during pregnancy due to placenta praevia.[14-16] Though trail of labour is recommended, mothers with a previous scar are rarely give the trail and are almost always planned for an elective c-section.

The association between c-sections and obese mothers has been well documented in the literature. Obese mothers are associated with complications such as diabetes (both gestational and pre-existing), pregnancy induced hypertension and pre-eclampsia are at a greater risk to deliver by c-section.[11,12,17-20] Our study revealed similar results, suggesting highly significant association between obesity and c-sections (p value = 0.000349).

Mothers who delivered preterm (<37 weeks gestation) or post term (>40 weeks gestation) were more likely to deliver by c-section compared to mothers who delivered at term. These results were in line with observations of Al Busaidi et al, Patel et al, and Bettegowdaet al.[13,14,21]

Maternal height <145 cm was found to be a risk factor for c-section delivery. 63.5% of mothers with height <145cm underwent c-section. Maternal short stature has been established as an independent risk factor for caesarean delivery.[22-24] WHO recommends mothers with height <140cm be categorized as at risk mothers. Kirchengast et al, Sheiner et al support this association with their studies.

The association between maternal education and risk of c-section has been described by numerous authors,[10,25,26] although some authors could not find such correlation.[8,27] Parazzini et al suggests that when adjusted for maternal age and birth weight, the association between maternal education and c-section markedly decreases. Our study did not show significant association between maternal education and c-section.

Some authors suggest significant association between socio-economic status and place of residence with c-section.[28-30] However, our study could not show them as risk factors for c-section. This might be due to the demographic distribution and geographical difference of the study sample as most of the mothers hail from a rural background. The same is true with maternal age as a risk factor for c-section. Though several studies implicate maternal age as a significant factor for c-section, our study could not make the association.

CONCLUSION:

In conclusion, these analyses have revealed several important associations between maternal risk factors and Caesarean section. Most of these factors are modifiable, and if targeted early can reduce the chances of caesarean section significantly.

It is interesting to note that c-sections are more common in primigravida mothers when compared to multi gravida. Also, mothers with a previous history of c-section are 14 times more likely to deliver again by c-section. This could be due to the fact that trail of labour is rarely given in mothers with a c-section scar. Although, studies from all over the globe showed promising results with vaginal births after caesarean section (VBAC), it is seldom practiced. One of the factors favouring a successful VBAC is a previous vaginal delivery. However, since primi mothers are already predisposed to c-section their chance of a successful VBAC is further diminished. Further studies to check the mode of delivery in primigravid

mothers is advocated. It is also essential to understand the factors in a primi mother that predisposes her to a c-section delivery.

Interventions in the form of legislation and policy making are required to regulate and check the proportion of c-section deliveries. Recently, the govt of Kerala issued guidelines to reduce the rate of c-section in the state of Kerala. Likewise, initiative in this regard is recommended by other states with high rates of c-section too.

LIMITATIONS OF THE STUDY:

There are a few limitations of the current study:

1. Due to the study setting being a single tertiary care teaching hospital, institutional factors that are responsible for caesarean sections were not comparable.
2. The authors acknowledge the fact that multivariate analysis would be best suited to analyse such study design.

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Research Article

Study of Biochemical Parameters in Rheumatoid Arthritis and Systemic Lupus Erythematosus

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ABSTRACT

Dynamic tissue that is remodeled constantly throughout life. The arrangement of compact and cancellous bone provides a strength and density suitable for mobility. In addition, bone provides a reservoir for calcium, phosphorus, magnesium and other ions necessary for homeostatic functions. Dead bone must be resorbed, and new bone must be formed. The purpose of this study was to evaluate the parameters like calcium, phosphorus, magnesium, alkaline phosphatase and its isoenzymes in RA and systemic SLE. A study was conducted in rheumatoid arthritis, pre and post-menopausal women with RA and systemic lupus erythematosus patients and controls. The serum calcium was decreased, while phosphorus and alkaline phosphatase were increased in rheumatoid arthritis and systemic lupus erythematosus patients as compared to control subjects. The isoenzymes of alkaline phosphatase showed one diffuse band which was originated from bone. Low serum calcium and high phosphorus and alkaline phosphatase (ALP) indicate that SLE & RA patients had sick bone. The serum ALP isoenzyme (bone) is a biochemical marker for the assessment of bone mineralization and monitoring the therapy with bisphosphonates which are bone strengthing agents.

KEY WORDS: bisphosphonates, isoenzymes, rheumatoid arthritis, systemic lupus erythematosus

INTRODUCTION:

A reduction of bone mass (or density) or the presence of a fragility fracture is prevalent among postmenopausal women but also occurs in men and women with underlying conditions or major risk factors associated with bone demineralization. It occurs with increasing age as bone tissue is progressively lost. In women, the loss of ovarian function at menopause precipitates rapid bone loss. Magaro et al have concluded that bone demineralization in rheumatoid arthritis (RA) is observed even in non-corticosteroid treated patients; articular lesions with subsequent reduction in physical activity appear to play an important role in axial bone loss in RA.[1] Stridl et al examined red cell magnesium and calcium content in patients with disorders of bone metabolism. The results indicated the important role of magnesium in these disorders of bone metabolism.[2] Yoshikawa et al have studied the combined effects of1- alpha (OH)D3 with calcium supplement in preventing progressive decrease of bone mass in patients with osteoporosis. The combine use of calcium and 1-alpha (OH) D3 had significant effect in preventing bone loss. Calcitonin has been considered to be useful in the treatment of bone demineralization due to its remarkable action on bone resorption as well as effect on bone formation.[3] Yashikawa et al have suggested that the use of calcitonin with calcium supplements had the place in the treatment of osteoporosis.[4] Eggelmeijer et al have concluded that long term treatment with an orally administered bisphosphonate overcomes bone loss and increases bone mass. This finding may have significance with regard to the treatment of patients with RA. The study of minerals, alkaline phosphatase and its isoenzymes play an important role in postmenopausal osteoporosis in RA.[5] Romagnoll et al have concluded that

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postmenopausal women had significantly higher levels of bone specific isoenzyme of alkaline phosphatase. Alkaline phosphatase levels were elevated in both serum and synovial fluid from RA patients.[6] Bone type alkaline phosphatase derived from synovial tissue may contribute to the raised activities of alkaline phosphatase in RA patients.[7] Abrahamsen and Harvey reviewed the evidence for vit. D supplementation in the management of patients with rheumatic diseases.[8]

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of unknown aetiology predominantly affecting women in their reproductive years. Many patients with SLE have to be treated with systemic glucocorticoids for prolonged periods of time. Osteoporosis is a frequent complication of SLE.[9]

The aim of the present study was to estimate serum calcium, phosphorus, magnesium and alkaline phosphatase and separation of serum alkaline phosphatase isoenzymes by electrophoresis in RA & SLE patients. The evaluation of these parameters on specific therapy such as supplementation of calcium, vit.D, calcitonin, bisphosphonates, hormone replacement therapy and exercise.

MATERIALS AND METHODS:

Institutional Ethics Committee approval was taken before conducting this study. Blood samples were collected from the patients admitted to the hospital suffering from rheumatoid arthritis and systemic lupus erythematosus.

RA patients with age over 50 years were included(cases n=40, control n=40). Some patients were on specific therapy like calcium, Vit D, diet advice, exercise, etc. Patients suffering from other co-morbid conditions, which are common in RA were excluded from this study.

Women suffering with RA between 40 to 50 years were considered for pre-menopausal group and women suffering with RA above 50 having menopause were considered for post-menopausal group(cases n=32, control n=32).

Female patients with known SLE were selected irrespective of their ages (Cases n=08, control n=10).Patients with any concomitant medical problems or those on any medications were excluded from the study.

40 control samples and 40 samples of the concerned patients were collected in plain bulb and allowed to clot at room temp. It was centrifuged at 3000 rpm for 10 minutes. The serum was separated and kept in the refrigerator at -20^{0}C till analyzed. All chemicals used were of analytical grade. Each parameter was standardized. Serum calcium was estimated by the method of Trindar.[10] Serum phosphorus was estimated by the method of Fiske and Subbarow.[11] Serum magnesium was estimated by the method of Titan yellow (Neill and Neely).[12] Alkaline phosphatase was estimated by the method of Kind and King[13]Alkaline phosphatase were separated by the method of Smith et al (1968)[14]. The statistical analysis was done by measuring mean , standard deviation and 't' test.

RESULTS:

Serum calcium levels were significantly decreased ($p \leq 0.001$) in rheumatoid arthritis patientsas compared to control subjects, while serum alkaline phosphatase levels were increased significantly ($p \leq 0.05$) than control subjects. The serum phosphorus levels were increased non significantly ($p > 0.05$) than controls, whereas there were a significant increase ($p \leq 0.001$) in magnesium levels than controls (Table 1).

The serum calcium levels were significantly decreased ($p \leq 0.01$) than control. The serum alkaline phosphatase levels were increased but non significantly ($p>0.05$) than controls. Serum phosphorus levels were decreased non significantly ($p > 0.05$) than controls, whereas there were no significance seen in serum magnesium levels than controls ($p> 0.05$) (Table 2).

The serum calcium levels were decreased non significantly ($p> 0.05$) and magnesium levels were decreased significantly ($p \leq 0.05$) as compared to control subjects in systemic lupus erythematosus. The serum alkaline phosphatase levels were increased but non significantly ($p> 0.05$) while serum phosphorus levels were increased significantly ($p \leq 0.05$) (Table 3).

Various methods are available to identify the isoenzymes of alkaline phosphatase. Polyacrylamide slab gel electrophoresis is the necessary means to separate various isoenzymes of alkaline phosphatase. The mobilities of the isoenzymes are as shown in photographs.

There were two bands present in the control group. Bone and liver isoenzymes are always present, one was originated from bone and the other was originated from liver (Figure 1).

There was appearance of only one band and that was diffuse as compared to control. The diffuse

Table 1: Biochemical parameters in rheumatoid arthritis (Male and Female)

Parameters	Control(n=40) Mean ± S.D	Rheumatoid Arthritis(n=40) Mean ± S.D	t-values
Calcium mg/dl	9.90 ±0.631	9.26 ±0.667	4.40***
Alkaline Phosphatase KA units	3.85 ±0.845	4.359 ±1.143	2.26*
Phosphorous mg/dl	3.68 ±0.544	4.027 ±0.673	2.53NS
Magnesium mg/dl	2.240 ±0.397	3.019 ±0.395	8.79***

***= p ≤ 0.001 *= p≤0.05 NS=Not Significant

Table 2: Biochemical parameters in pre and postmenopausal women with RA (Female).

Parameters	Control(n=32) Mean ± S.D	Pre and post -menopausal women(n=32) Mean ± S.D	t - values
Calcium mg/dl	10.06 ±0.773	9.248 ±0.635	4.59**
Alkaline Phosphatase KA units	3.70 ±0.798	4.10 ±1.17	1.59 NS
Phosphorous mg/dl	3.872 ±0.542	3.98 ±0.655	0.72 NS
Magnesium mg/dl	2.60 ±0.533	2.896 ±0.448	2.40 NS

**= p ≤ 0.01 NS=Not Significant

Table 3: Biochemical parameters in systemic lupus erythematosus.

Parameters	Control(n=10) Mean ± S.D	Systemic Lupus Erythematosus(n=08) Mean ± S.D	t-values
Calcium mg/dl	10.15 ±0.858	9.11 ±1.59	1.78 NS
Alkaline Phosphatase KA units	3.57 ±0.759	4.471 ±1.07	2.09 NS
Phosphorous mg/dl	4.075 ±0.380	4.722 ±0.657	2.62*
Magnesium mg/dl	2.84 ±0.542	2.75 ±0.604	0.33*

*= p ≤ 0.05 NS=Not Significant

band appeared in all patients and this band was originated from the bone. The diffuseness was most striking (Figure 2).

There was appearance of only one band and that was diffuse as compared to control. The diffuse band appeared in all patients and this band was originated from the bone (Figure 3).

DISCUSSION:

In our study, calcium levels are significantly decreased in rheumatoid patients, whereas alkaline phosphatase levels are significantly increased as compared to control subjects. Serum phosphorus levels are increased non significantly than controls. Previous studies reported, the concentrations of serum calcium and phosphorus are usually reduced and serum alkaline phosphatase activity was elevated in RA patients.[15] Contrary to other studies we found serum magnesium levels increased significantly in RA patients. Chronic inflammatory conditions are likely to alter magnesium levels and possible mechanism of decrease magnesium in RA in other studies is due to chronic inflammation and autoimmune injury.[16]

Osteoporosis is a frequent complication of rheumatoid arthritis especially in post-menopausal women.[17] Clinical laboratory tests were used to evaluate individual for osteoporosis.[18]In our study we found significantly decreased serum calcium levels in post-menopausal and pre-menopausal women suffering with RA compared to control subjects. Many factors that may cause generalized osteoporosis in inflammatory arthritis include circulating pro-inflammatory molecules, hormones alter calcium metabolism and the effects of anti-rheumatic and anti-inflammatory drugs.[19] One previous study has concluded that low dose steroid therapy is associated with increased bone loss and number of fractures in patients with rheumatoid arthritis.[20] Sambrook et al

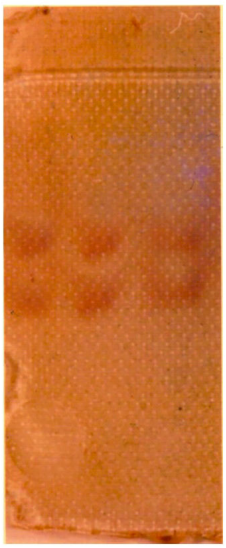

Figure 1: Shows the isoenzymes of alkaline phosphatase in control subjects.

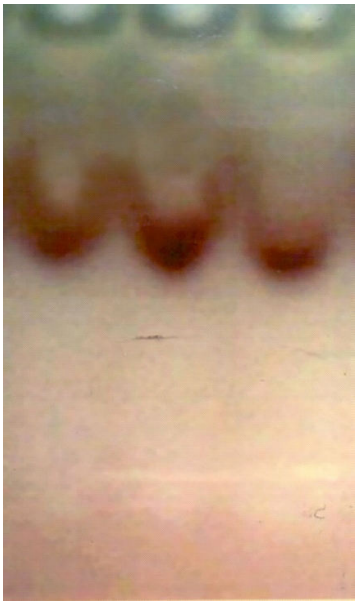

Figure 2: Shows the isoenzymes of alkaline phosphatase in rheumatoid arthritis patients.

have studied the magnitude and distribution of osteoporosis in RA. Bone mineral density (BMD) was measured by dual X-ray absorptiometry. They found that BMD was reduced at most skeletal sites with RA. Osteoporosis in RA is generalized and may be related to loss of mobility of muscle mass.[21]

Systemic lupus erythematosus results from tissue damage caused by pathogenic subsets of autoantibodies and immune complexes. In our study we get significantly higher serum phosphate levels & significantly lower serum magnesium levels in SLE patients as compared to control subjects.It is not

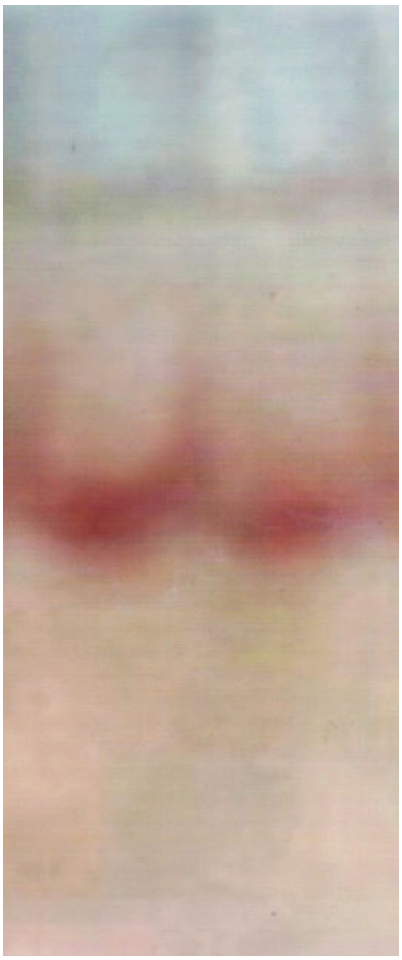

Figure 3: Shows the isoenzymes of alkaline phosphatase in systemic lupus erythematosus.

known why Mg levels tend to drop in patients with chronic pain problems such as SLE. It has been suggested that there may be a problem with Mg availability and/or utilization at the tissue level as opposed to a suboptimal dietary intake or an increased excretion of Mg.[22] The literature also suggests that corticosteroid treatment in SLE patients may even intensify the Mg deficiency.[23] Whatever the mechanism, Mg deficiency should not go unnoticed. To fail to consider Mg deficiency in the differential diagnosis of neuromuscular problems in SLE might expose such patients to undue risk and expense particularly if myalgias are mistakenly attributed to inflammation. Magnesium deficiency can cause complication such as osteoporosis.[24] SLE patients develop bone loss due to hypothalamo-pituitary gonadal dysfunction following corticosteroid therapy and ovarian dysfunction (SLE specific). This may be the cause of increased serum phosphorus levels in SLE patients.

In patients on steroids and calcium supplementation bone resorption must have decreased. Vitamin D is of benefit in both the treatment and prevention of steroid induced bone loss. In RA patients taking steroids, the addition of Vitamin D with elemental calcium had beneficial effects on bone density. Bisphosphonates are pyro-phosphate analogs that bind to hydroxyapatite at sites of active boneremodeling.[8] The study carried out on osteoporosis was not able to conclude that giving supplementation of folic acid, B6, B12 and other antioxidants could prevent osteoporosis due to insignificant results.[25] Some patients of RA and SLE were on calcium, phosphorus bisphosphonates which have given positive effect on bone mineral homeostasis.[26] Low calcium and high phosphorus indicates that patient had osteoporosis. For treatment of patients, attention was given to calcium, Vitamin D and bisphosphonates and also from natural sources like fruits.

The human alkaline phosphatase constitutes a system of multiple molecular forms of enzymes in which heterogeneity is partly due to genetic factors and partly to post translational modifications.[27] Raised serum alkaline phosphatase activity in RA has been reported.[28] Serum ALP isoenzymes were done by PAGE in patients with RA and SLE. The rise in serum ALP is due to the specific bone isoenzyme which is diffuse band that is responsible for the rise in serum ALP. The serum isoenzymes are biochemical markersfor the assessment of osteoporosis and monitoring the therapy with bisphosphonates which are bone strengthening agents.

CONCLUSION:

We observed low calcium, high phosphorus and increased ALP in RA and SLE patients which indicates that patients had sick bone. Separation of the serum alkaline phosphatase by electrophoresis in RA and SLE showed one diffuse band. Appearance of diffuse band is because of rise in serum alkaline phosphatase levels. The rise in serum ALP in RA and SLE is due to bonespecific ALP isoenzyme. The serum isoenzyme is a biochemical marker for the diagnosis of rheumatoid arthritis and systemic lupus erythematosusand monitoring the therapy, with bisphosphonates, which are bone strengthening agents.

Hence, it is recommended to supplement calcium bisphosphonates & vitamin D in patients with RA. Along with above, magnesium is also recommended for SLE patients.

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Research Article

Total and Ionic Serum Calcium Level in Icteric Newborn Receiving Phototherapy

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ABSTRACT

Jaundice is the most common condition that requires medical attention in newborns. The study was conducted on 100 neonates (42 preterm and 58 term) presenting with neonatal hyperbilirubinemia requiring phototherapy. Only normal neonates were included in study. Measurement of total and ionic serum calcium levels was done before and after 48 hours of institution of phototherapy. The sample collected before the start of phototherapy was taken as control. After 48 hours of phototherapy there was a statistically significant fall in total and ionic serum calcium levels in 54 % neonates. It was observed that hypocalcemia was more common in preterms (67%) than term (45%) neonates after receiving phototherapy for 48 hours. The present study shows hypocalcemia was more common in preterms and term newborns having higher total serum bilirubin levels. A statistically significant difference was observed in total calcium levels between TSB groups 15.1-20 and 20.1-30 mg/dl. The neonates were clinically assessed for features of hypocalcemia and it was found that preterms developed more symptoms of hypocalcemia than term neonates. Jitteriness was the most common symptom observed. It was concluded that phototherapy induced hypocalcemia is a significant problem. Thus, calcium supplementation may be considered especially in neonates with higher range to total serum bilirubin.

KEY WORDS: hyperbilirubinemia, hypocalcemia.phototherapy,

INTRODUCTION:

Neonatal hyperbilirubinemia is cause of concern for the parents as well as the paediatricians. Early discharge of healthy term newborns after delivery had become a common practice because of medical and social reasons and economic constraints. It is significant that most common cause of readmission during the early neonatal period is hyperbilirubinemia.[1]

Adults appear jaundiced when the serum bilirubin levels is >2mg/dl, and newborn appear jaundiced when it is >7 mg/dl.[2] However hyperbilirubinemia in the newborn period can be associated with severe illness such as haemolytic disease, metabolic and endocrine disorders, anatomic abnormalities of the liver and infection. Unconjugated hyperbilirubinemia is the most common form of jaundice encountered by doctors. Common risk factor for hyperblirubinemia include fetomaternal blood group incompatibility, prematurity and previously affected sibling. Cephalhemotomas, bruising and trauma from instrumental delivery may increase the risk for serum bilirubin elevation.[3]

The aim of phototherapy is to prevent potentially toxic bilirubin level to reach central nervous system and to decrease the need for exchange transfusion. Decision for therapy depends on factor such as actual bilirubin level and its rate of increase, weight and length of gestation at birth, post natal age and presence of factor that influence bilirubin albumin level. Phototherapy and, if it in unsuccessful, exchange transfusion remain the primary treatment modality.[4]

The commonly known side effects of phototherapy are loose stool, hyperthermia, dehydration, skin burn, photoretinitis, low platelet count, increased red cell osmotic fragility, bronze baby syndrome, riboflavin deficiency, and DNA damage.[2] A lesser known but potential complication of

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phototherapy is hypocalcemia.[4]

In 1979, Romagnoli et al suggested the association of hypocalcemia with phototherapy in preterm newborns.[5] In 1981, Hakanson and Bergstrom also observed hypocalcemia in newborn rats.[6] Sethi et al in 1993 observed decrease in total calcium levels in 90% preterm and 75% term neonates after 48 hours of phototherapy.[4]

Several studies showed hypocalcemic effect of phototherapy (Jain et al,1998; Eghbalian F and Moncef A, 2002; Karamifar et al, 2002; Medhat FB,2006; Yadav et al,2012; Sajjadian et al, 2013; Tehrani et al and Bahbah et al, 2014)[7-14].

Neonatal hypocalcemia is defined as total serum calcium concentration < 7 mg/dl or ionized calcium concentration < 4 mg/dl (<1mol/l). In VLBW infants ionized calcium values of 0.8 – 1 mmol/l are common and not usually associated with clinical symptom. Assessment of calcium status using ionized calcium is preferred, especially in first week of life. Correction nomogram used to convert total calcium into ionized calcium are not reliable.[2]

Hypocalcemia symptoms include neuromuscular irritability like myoclonic jerks, jitteriness, exaggerated startle and seizures. Hypoclacemia may cause tachycardia, heart-failure, prolonged QT interval, decreased contractility. Apnea, cyanosis, tachypnoea, vomiting and laryngospasms are other symptoms that are noted. Ionized calcium is crucial for many biochemical processes, including blood coagulation, neuromuscular excitability, cell membrane integrity and function, and cellular enzymatic and secretory activity.[2]

The decrease in calcium due to phototherapy can be explained by melatonin secretion. Melatonin stimulates secretion of corticosterone, which decreases calcium absorption by bones. Phototherapy leads to inhibition of pineal gland by transcranial illumination, resulting in decline of melatonin level and as a result, hypocalcemia develops.[9]

Cortisol exerts a direct hypocalcemic effect by decreasing the absorption of Calcium and phosphate ions from the intestine by antivitamin D action and by increasing the renal excretion of these ions and also accelerates the bone uptake of calcium.[15]

Most of the studies done till now had observed only serum total calcium levels. Only one study by Yadav et al. in 2012 considered changes in ionic calcium with phototherapy but they did not observed total calcium. Moreover, none of the studies had considered neonates with ABO-Rh incompatibility.

The present study was thus undertaken to include neonates with ABO-Rh incompatibility and to assess the effect of phototherapy on serum total and ionic calcium in preterm and term neonates with hyperbilirubinemia.

MATERIALS AND METHODS:

This study was conducted from July 2014 to October 2015 at Sick Newborn Care Unit (SNCU) of Department of Pediatrics , M.L.B. Medical College, Jhansi with active collaboration of Department of Obstetrics and Gynaecology, after taking approval from the institutional ethical committee. The study was conducted on 100 neonates (42 preterm and 58 term) presenting with neonatal hyperbilirubinemia requiring phototherapy.

Only normal neonates were included in study. Any neonate who had or developed complication during the course of study were excluded. Newborn infants with neonatal jaundice who were managed with exchange transfusion were also excluded.

All the neonates included in our study having Hyperbilirubinemia were managed with phototherapy (Decided on 'American Academy of pediatrics, 2004')(Table 1 and Table 2).[16]

All the cases were evaluated by detailed history, clinical examination and laboratory investigation. Every case was investigated for serum total and ionic calcium (at zero hour and at 48 hours of phototherapy), serum bilirubin, blood group, and Rh typing, reticulocyte count, Hemoglobin, peripheral blood smear, sepsis screen, other electrolytes and renal function tests. Mothers were examined for their blood group and Rh typing.

Both serum total and ionic calcium was determined by calorimetric method using standard calorimetric test kits (with the help of auto analyser Beckman Coulter AU analyser). The reagent used for estimating total calcium was Arsenazo III and for ionic calcium was o-cresolphthalein complexone forming coloured complexes. Conjugated and unconjugated serum bilirubin was estimated by Malloy and Evelyn method by using diazo reagent. Thereafter, all data were tabulated and analyzed statistically to detect hypocalcemia as a complication of phototherapy. Statistical presentation and analysis of the present study was conducted by Student t-test and paired t-test.

RESULTS :

This study was carried out on 100 neonates (42 preterm and 58 term) over a period of 16 months. Out of 42 preterm neonates 17 (41%) were males

Table 1: Management of Hyperbilirubinemia in healthy term newborn.

Total Serum Bilirubin (mg/dl)				
Age (Hours)	Consider Phototherapy	Phototherapy	Exchange transfusion if phototherapy fails	Exchange transfusion and phototherapy
< 24 hrs	-	-	-	-
25 – 48	≥ 12	≥ 15	≥ 20	> 25
49 – 72	≥ 15	≥ 18	≥ 25	≥ 50
≥ 72	≥ 17	≥ 20	≥ 25	> 30

Table 2: Management of Neonatal hyperbilirubinemia in very low birth weight babies based on bilirubin level (mg/dl)

Weight (g)	Phototherapy	Consider exchange transfusion
500-750	5-8	12-15
750-1000	6-10	7-15
1000-1250	8-10	15-18
1250-1500	10-12	17-20
1500-2500	15-18	20-25

Table 3: Pre study and post study values of total calcium (mg/dl) in preterm and term neonates.

	PRETERM - Total serum calcium (mg/dl) [Mean±SD]			TERM - Total serum calcium(mg/dl) [Mean±SD]		
Prestudy	9.5009± 0.6510			9.6456 ± 0.7422		
Poststudy	8.7777± 1.3359			9.1496 ± 1.0066		
Significance	p<0.05	df=82	t=3.15	p <0.05	df= 114	t=3.02

while 25 (59%) were females and out of 58 term babies 39 (67%) were males and 19 (33%) were females. The ratio of male:female among preterm neonates is 0.68:1 while it is 2:1 in term neonates. Overall the male:female ratio is 1.3:1. 57 neonates (57%) were weighing more than 2500 grams, 33 (33%) were low birth weight and 10 (10%) were very low birth weight. According to the mode of delivery 22 (52%) preterm neonates were born through normal vaginal route while 20 (48%) by LSCS. In term babies 34 (58%) were born by normal route while 24 (42%) by LSCS. Most of the neonates (66) were having TSB between 15.1 and 20 mg/dl while 11 neonates were in TSB range 10.1 and 15.0 mg/dl, 22 were in TSB range 20.1 and 30.0 and only one neonate was having TSB more than 30 mg/dl. 10 preterm (24%) out of 42 and 18 term (31%) neonates were having ABO or Rh incompatibility but none of the baby was having both types of incompatibility. Overall 28 (28%) of the neonates in our study was having either ABO or Rh incompatibility. Most of the cases, 24 (57%) preterm and 36 (62%) term have onset of jaundice after 72 hours while none of the cases presented before 24 hours.

Table 4: Pre study and post study values of Ionic calcium (mmol/l) in preterm and term neonates.

	Preterm - Ionic serum calcium (mmol/l) [Mean±SD]			Term - Ionic serum calcium (mmol/l) [Mean±SD]		
Prestudy	1.0954 ± 0.1036			1.1053 ± 0.1182		
Poststudy	0.9819 ± 0.1323			1.0420 ± 0.1231		
Significance	p<0.05	df=82	t=4.37	p<0.05	df= 114	t=2.82

Table 5: Total serum calcium values before and after phototherapy in different TSB range.

TSB Range (mg/dl)	No of Neonates	Total Serum Calcium (mg/dl)		
		Before phototherapy	After phototherapy	p value (<0.05)
10.1 -15	11	9.540 ±0.548	8.257 ±1.128	0.0029
15.1 -20	66	9.312 ±0.631	8.611 ±1.302	0.0001
20.1 -30	22	9.641 ±0.744	7.814 ±1.570	0.0001
>30	01	10.9	6.8	

Table 6: Serum Ionic calcium values before and after phototherapy in different TSB range.

TSB Range (mg/dl)	No of Neonates	Ionic Calcium (mmol/l)		
		Before phototherapy	After phototherapy	p-value (<0.05)
10.1 -15	11	1.178 ±0.112	0.978 ±0.126	0.0008
15.1 -20	66	1.073 ±0.104	0.956 ±0.132	0.0001
20.1 -30	22	1.124 ±0.128	0.902 ±0.104	0.0001
>30	01	1.37	1.10	

Table 7: Distribution of cases according to symptoms in symptomatic hypocalcemic neonates.

Symptom	Preterm neonates having hypocalcaemia		Term neonates having hypocalcaemia	
	No	%	No	%
Jitteriness	14	50	10	38
Irritability/Excitability	6	21	6	24
Lethargic	6	21	4	15
Convulsion	0	0	0	0
Total	26	92	20	77

It was found that out of 42 preterm neonates 28 (67%) developed hypocalcemia. While out of 58 term neonates only 26 (45%) developed hypocalcemia. Overall 54 (54%) of icteric newborns developed hypocalcemia after 48 hours of phototherapy (Table 3 and Table 4).

It was observed that there was a statistically significant fall in total and ionic serum calcium levels in neonates in different total serum bilirubin range after phototherapy. Decrease in serum calcium (Total and Ionic) in all groups was found to be statistically significant (p<0.05) (Table 5 and Table 6).

The fall in serum total and ionic calcium among groups with TSB range 10.1-15 and 15.1-20 was not found to be significant (p=0.39) and (p=0.60). The fall in serum total calcium among groups with TSB range 15.1-20 and 20.1-30 was found to be significant (p=0.02) but fall in ionic calcium among these groups was not significant (p=0.08).

Further studies are needed to confirm significant difference in fall in ionic calcium among different TSB range groups. Out of 28 preterm neonates that developed hypocalcemia after exposure to phototherapy, 26 (92%) became symptomatic. Similarly, out of 26 term neonates that developed hypocalcemia 20 (77%) became symptomatic. Jitteriness was the most common symptom in both groups and none developed convulsions (Table 7).

DISCUSSION :

Jaundice is an important problem in the first week of life. Jaundice is attributable to physiological immaturity of neonates to handle increased bilirubin production. The use of phototherapy has decreased the need for exchange transfusion in term and preterm infants with hemolytic and nonhemolytic jaundice. When indication for exchange transfusion are present phototherapy should not be used as a substitute however, phtototherapy may reduce the need for repeated exchange transfusion in infants with hemolysis.[17]

Our study was carried out on 100 neonates (42 preterm and 58 term). The first samples collected before the start of phototherapy acted as control. Neonates presenting with hyperbilirubinemia were subjected to phototherapy for 48 hours and levels of serum total and ionic calcium were observed.

Jain BK et al. in 1998 studied 20 term and 20 preterm icteric neonates and observed hypocalcemia in 55% preterm and 30% term neonates after 48 hours of phototherapy.[7]

Study done by Medhat FB et al. in 2006 on 20 term and 20 preterm neonates observed hypocalcemia in 95% preterms and 75% term neonates after 48 hours of phototherapy.[10] Study done by Yadav RK et al. (2012) took 15 preterm and 15 term neonates and 20 neonates were taken as control (10 preterm and 10 term). They observed hypocalcemia in 80% preterm and 66.6% term neonates.[11]

Latest study was done in 2014 by Bahbah et al. at the Menaufia University, Egypt. They studied only 50 full term neonates with jaundice (25 males and 25 females) who received phototherapy for treatment of neonatal indirect hyperbilirubinemia and 25 neonates complaining of physiological hyperbilirubinemia taken as controls not exposed to phototherapy. After 48 hours of phototherapy hypocalcemia was found in 13 (26%) neonates and 37 cases (74%) had normal calcium levels.[18]

Study by Yadav et al. (2012) observed that all the hypocalcemic preterm neonates became symptomatic and 80% term babies became symptomatic while in our study 2 preterm hypocalcemic neonates remained asymptomatic, while 77% term neonates became symptomatic. Jitteriness remained the most common manifestation of hypocalcemia.[11] Study by Eghbalian F (2002) observed only one case of symptomatic hypocalcemia in the form of apnea in a term baby.[8] Study by Bahbah et al. (2014) showed jitteriness as the most common symptom of hypocalcemia while some cases developed convulsions.[18]

Hakanson DO et al. in 1987 reported that when young rats were exposed to white fluorescent light, the serum concentration of calcium did decrease. He showed that this calcium drop was accompanied by a decrease in serum melatonin concentration. This effect can be prevented by shielding the output, by inhibiting corticosterone synthesis, and by administration of endogenous melatonin. Light induced hypocalcemia may result from increased calcium uptake by bone when the blocking effect of melatonin decrease after pineal inhibition by transcranial illumination.[6]

The efficacy of phototherapy in prevention and treatment of hyperbilirubinemia in new born infants has been well established. In the present study all our neonates responded to management with phototherapy. All those neonates who were in need of exchange transfusion but could not be done due to unavailability of blood, also responded well to phototherapy. In this study a significant fall in total and ionic serum calcium levels was observed after phototherapy. Hypocalcemia was observed in larger percentage of preterm neonates as compared to full term neonates. The present study show that there is significant fall in total and ionic serum calcium levels in neonates in different TSB range groups after phototherapy. As the serum bilirubin increases there is a significant fall in total calcium levels among different TSB range groups (TSB 15.1-20 mg/dl and TSB 20.1-30mg/dl). But further studies are needed to confirm significant difference in fall in ionic calcium among different TSB range groups.

CONCLUSIONS:

A significant fall in total and ionized serum calcium levels was observed in icteric neonates after 48 hours of phototherapy. The present study shows hypocalcemia was more common in preterms than term newborns. There is greater fall in total and ionic serum calcium levels at higher total serum bilirubin levels. A statistically significant difference was observed in total calcium levels between TSB groups 15.1-20 and 20.1-30 mg/dl. On clinical assessment preterms developed more symptoms of hypocalcemia than term neonates. Jitteriness was the most common symptom observed. Hypocalcemia in neonates was managed with intravenous calcium gluconate and none required anticonvulsants. All of our neonates responded to management with phototherapy and none of them required exchange transfusion, got improved and discharged. This study shows that neonates under phototherapy are at high risk of hypocalcemia.

It is concluded that phototherapy induced hypocalcemia is a significant problem and hence calcium supplementation to these babies may be considered.

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Research Article

Clinical Profile of Patients with Status Epilepticus from Rural Area

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ABSTRACT

Status epilepticus (SE) is a neurological emergency associated with significant morbidity and mortality, if not treated effectively in time. An attempt was made to generate the baseline data regarding the etiologies and clinical profile of SE. A total of 50 patients diagnosed on clinical grounds as SE were analyzed for different parameters. SE was found more common in males and in the age group 21-40 years. Most common etiology was acute symptomatic (68%). Seven patients subjected to lumbar puncture and CSF analysis revealed TB meningitis (three), viral etiology (three) and pyogenic meningitis (one). Of the 50 patients, 44 (88%) responded to the first-line drugs and six (12%) patients required second-line drugs. Five patients (10%) succumbed to death due to massive intra-cerebral bleeding (two), endosulfan poisoning (one), Japanese encephalitis with refractory SE (one) and primary epilepsy with intractable seizures (one). Age, gender and etiology of SE were found to be non-significant. Results indicate that SE can occur in epileptic as well as non-epileptic individuals. Early recognition, good knowledge of various etiologies, prompt initiation of therapy and availability of ventilatory facility as well as ICU care is of paramount importance in the management of SE.

KEY WORDS: clinical profile, rural area, status epilepticus

INTRODUCTION:

Status epilepticus (SE) is a major neurological emergency, which can cause significant morbidity and mortality, if not treated effectively in time. SE is a term used to describe a prolonged and self-sustaining seizure that may have overt, subtle, or almost no behavioural manifestations. It may be regarded as the most extreme form of epilepsy, or as an expression of an acute and often life-threatening brain disorder,such as stroke or encephalitis.

The diagnosis of SE is not difficult when motor signs are overt. However, these motor signs are seen in some of the patients only and other clinical types still pose serious diagnostic challenges such as subtle SE, complex partial SE and Non-convulsive status-epilepticus. Age-specific incidence rates of SE show a U-shaped curve with a bimodal distribution peaking in very young and the elderly.[1]

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Its aetiology varies among the different age groups. The aetio-pathologies may be heterogeneous, which may vary with time, cultural and environmental factors.[2] A periodic analysis is therefore necessary to know the current trends of the aetiology of SE. Due to the dearth of information on aetiologies, response to current treatment guidelines and outcome of SE; this study was conducted to generate the baseline data which pertained to the aetiologies and the clinical profile of SE in our region.

MATERIALS AND METHODS:

The present study was carried out in a tertiary care hospital. The study protocol was approved by ethical committee of Govt. Medical College, Latur. A total of 50 cases admitted in Emergency Ward and ICU, diagnosed on history and clinical grounds as status epilepticus were included in the study, after taking informed and written consent from close relative. The patients with non- convulsive status epilepticus, pseudoseizures and patients below 12 years of age were excluded from the study. The patients with continuous seizure of more than five minutes duration or two or more discrete seizures of five minutes duration between which there was an

incomplete recovery of consciousness were subjected to a detailed recording of their history, neurological examinations and routine investigations which included a haemogram, renal and liver function tests, blood sugar level, arterial blood gas analysis and a metabolic profile assessment including serum calcium and magnesium. Lumbar puncture were done after controlling the seizures. All the patients were treated with intravenous lorazepam and phenytoin according to the protocol- intravenous lorazepam (0.1 mg/kg), followed by the intravenous loading of phenytoin (20 mg/kg) as the first-line drug treatment. If the seizure did not stop within 30 minutes of the starting of the loading dose of phenytoin, the patients were given additional intravenous phenytoin (5 mg/kg). Patients already on valproate therapy were given loading dose of valproate (25-30mg/kg). The second line drugs were given when no response was observed with the above drugs in the first hour. The second line drugs were- an intravenous loading dose of valproate (25-30 mg/kg) (if not given earlier) or phenobarbitone (20 mg/kg) as the loading dose, followed by a maintenance drip (60 mg/min) till the seizures were under control or till one hour, whichever was earlier. If the seizures could still not be controlled after one hour (refractory seizures), thiopentone (10-20 mg/kg) as a loading dose, followed by an infusion (0.5-1.0 mg/kg/hr) was given along with mechanical ventilatory support. In addition, the patients received appropriate treatment for the underlying disease. Those patients who failed to respond to the initial lorazepam and the loading dose of phenytoin were defined as non-responders.

STATISTICAL ANALYSIS:

In univariate analysis, age was analysed as a continuous variable, and the etiology, sex, response to treatment were analysed as categorical variables. The variables studied for statistical significance included age, sex, duration of SE, etiology, response to first line treatment and 30 day mortality.

RESULTS:

In this study, maximum number of cases were found in the age group 21-40 years (n=24) followed by 11-20 years age group (n= 8). The youngest patient was 13 years old and oldest was 75 years old. Mean age was 40 years ±17.2 years. Out of the 50 cases, 23 (46%) were female and 27 (54%) were males. Male to female ratio was found to be 1.2:1.

The etiology was acute symptomatic in 68% patients, remote symptomatic in 6 % patients and cryptogenic in 4 % patients. Eleven patients were identified as established epileptics with poor drug compliance. Amongst these five patients missed the anti-epileptic drug (AED) treatment due to forgetfulness. Four had financial limitations in continuing the drugs and two stopped the medicines due to ignorance. In the acute symptomatic SE patients, CNS infections were the commonest etiology (n=19 patients). Neurocysticercosis (NCC) was found to be the most frequent infection, followed by meningo-encephalitis. In the vascular etiology of symptomatic SE, haemorrhagic stroke was found to be the commonest cause (n=5). One patient had cerebral venous sinus thrombosis. Six patients had SE due to metabolic disorders. Hyperglycaemia (n=1), hyponatraemia (n=1), endosulfan poisoning (organochlorine insecticide) (n=1), organo-phosphorus poisoning (n=1), alcohol withdrawal (n=1) and hypoxic brain injury (n=1) (Table 1).

Out of 50 patients, seven clinically indicated patients who had the clinical signs of meningeal irritation were subjected to lumbar puncture and CSF analysis was done. Out of these seven patients, one had findings which were suggestive of pyogenic meningitis, whereas three had TB meningitis. Three patients had mild lymphocytic pleocytosis with a mild increase in proteins, which was suggestive of viral etiology (Graph 1).

Of the 50 patients with SE, 44 (88%) responded to the first-line drugs and six (12%) patients required second-line drugs. The variables which were studied to predict the response to the first-line drugs included etiology and the duration of SE. The non-responders in acute symptomatic SE were 14.7% as compared to 6.3% in other etiologies. The duration of SE and the delay in starting the treatment in all of the non-responders were more than 24 hours. None of the patients who presented after 48 hours of duration of SE responded to first line AEDs. Thus, the statistically significant predictor of non-responsiveness to 1st line AEDs in patients with SE was duration of status epilepticus. Etiology of SE was found to be non-significant (Table 2).

In the present study, mortality was 10% (n=5). Four out of five deaths were seen in the acute symptomatic group, two of them being cases of massive intra-cerebral bleeding, one patient of endosulfan poisoning and one had Japanese encephalitis with refractory SE. The fifth death fell into the established epilepsy group whose SE was of

Table 1: Etiologies of SE

Etiology	No. of patients	Subgroup	Disease
Acute symptomatic	34	CNS infections (19)	Neurocysticercosis :NCC (10) Meningencephalitis(5) Tuberculoma /TBM(3) Pyogenic meningitis (1)
		Vascular (9)	Haemorrhagic CVA (5) Non- haemorrhagic infarct (3) Cerebral venous sinus thrombosis (1)
		Metabolic (6)	Poisoning (2) Hypoglycaemia (1) Hyperglycaemia (1) Alcohol intoxication (1) Hypoxia (1)
Remote symptomatic	3	--	Old stroke with gliosis (2) Small calcific lesion (1)
Established epilepsy	11	--	--
Cryptogenic	2	--	--

Table 2: Response to AEDs in SE

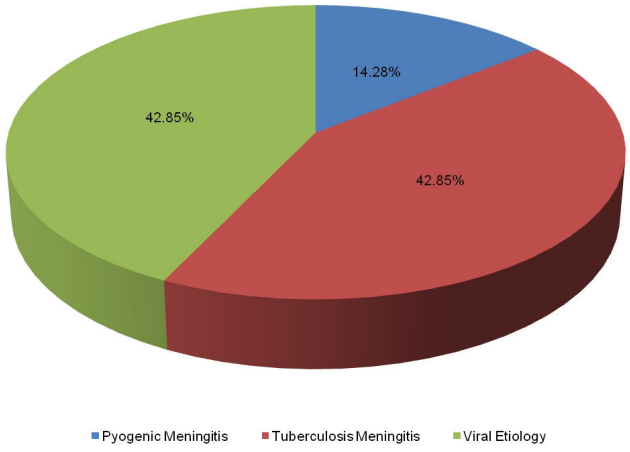
Variable	Responders to first line AED	Non-responders to first line AED	X^2	*p*- value
Etiology				
Acute symptomatic	29 (85.3)	05 (14.7)	0.737	> 0.05 (Not significant)
Other etiologies	15 (93.7)	01 (6.3)		
Duration of SE				
< 24 hours	38 (100)	00	35.795	<0.001 (Highly significant)
25 - 48 hours	06 (75)	02 (25)		
49 - 72 hours	00	04 (100)		

Note - Figures in parenthesis indicate percentages

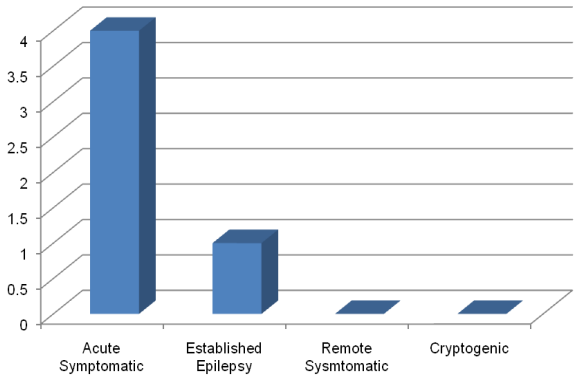
36 hours duration and he had primary epilepsy with intractable seizures, which caused acute renal failure and metabolic acidosis as terminal events (Graph 2).

Amongst the five patients who died, three were between 51-80 years of age. Out of five deaths, four were male and one was female. Five non-responders (83.34%) succumbed to death, whereas there was no mortality amongst the patients who responded to 1st line therapy. Two out of four (50%) patients who presented after 48 hours and three out of eight (37.5%) patients who presented between 25 to 48 hours died, whilst there was no mortality amongst the patients who presented within 24 hours of onset of convulsions. The statistically significant predictors of mortality in patients with SE were duration of status epilepticus and response to 1st line antiepileptic therapy. Age, Gender and etiology of SE were found to be non-significant (Table 3).

Graph 1: CSF Profile in SE.



Graph 2: Mortality



DISCUSSION:

Status epilepticus is a common medical emergency which accounts for 1% – 8% of all the hospital admissions for epilepsy.[3] The duration of SE and its etiology have been the important predictors of its outcome. In the developed countries, pre-hospital treatment protocols are available for the paramedics to reduce the duration of SE and to improve its outcome. However, no such protocols are available in developing countries like India.

The mean age of the patients with SE was 40 ± 17.2 years (13–75 years), 16% were in the younger age group (11-20 years) and 48% fell into the young adult group (21-40 years). These findings are in agreement with earlier studies from the developing countries, wherein a higher proportion of the patients with SE were either children or young adults (20–40 years) [4,5]. However, in the developed countries, a bi-modal peak has been described with a high incidence in infants and in the elderly.[6] The male to female ratio of 1.2:1 in the present study is similar to population based studies reported earlier.[7,8]

The most common etiology found was acute symptomatic (68%), which is comparable to studies from India[4,5] and most of the cases (38%) with SE caused by CNS infections is comparable with the earlier studies from developing countries[5,9], who have also reported similar etiological spectrum. Amongst the CNS infections, NCC was most common infection (10/19; 52.6%). This is also in concordance with the findings of Murthy *et al.* [4], in their study NCC accounted for 42.5% of the SE cases. Meningo-encephalitis accounted for the SE in five patients (26.3%) in our study, which was slightly lower than study from north India by Misra *et al.* [10] that reports one third of the SE cases caused due to meningo-encephalitis of which, nonspecific encephalitis was the commonest cause. We found out that the incidence of SE due to vascular etiology was 18% (9/50), out of which three patients had non haemorrhagic ischaemic stroke, five patients had haemorrhagic stroke and one patient suffered cerebral venous sinus thrombosis. A similar incidence (15%) of SE due to vascular etiology was also reported by Murthy *et al.* [4] A metabolic cause for SE was noted in 6 (12%) patients, which is quite similar to earlier studies.[4,5]

A total of 22% of the SE patients were established epileptics with poor treatment compliance, either due to forgetfulness or ignorance. The increased cost of the AED treatment and the intermittent drug supply were also the factors which were responsible for the noncompliance. A drug default was noted in 7.9% and 20% patients in studies by Kalita *et al.* [5] and Murthy *et al.* [4] respectively.

In the present study, 88% of the SE patients responded to the first-line drug treatment. The response rate was noted to be 50% and 88% in the studies by Kalita *et al*[5] and at Murthy *et al*[4] respectively. The non-responders were more in the acute symptomatic SE (15.4%) group as compared to those in other etiology groups (8.4%). CNS infection or haemorrhagic stroke was the common etiology amongst the non-responders, which was comparable to that in other studies. [5, 9-11] The duration of SE before the treatment in all the non-responders was more than 24 hours, which was similar to the observation made by Murthy *et al.* [4] In their study, duration and acute symptomatic etiologies were the independent predictors of no-response to first-line drugs. In our study only duration of SE was found to be statistically significant.

Table 3: Predictors of death following convulsive status epilepticus.

Variable	No. of cases	No. of deaths	X^2	*p*- value
Age				
11 – 30 years	17 (34)	01 (5.8)	2.98	> 0.05 (Not significant)
31 – 50 years	21 (42)	01 (4.76)		
51 – 80 years	12 (24)	03 (25)		
Gender				
Male	27 (54)	04 (14.8)	1.512	> 0.05 (Not significant)
Female	23 (46)	01 (4.34)		
Response to 1st line of treatment				
Responders	44 (88)	00	22.000	< 0.001 (Highly significant)
Non-responders	06 (12)	05 (83.34)		
Duration of SE				
< 24 hours	38 (76)	00	12.467	< 0.05
25 - 48 hours	08 (16)	03 (37.5)		
49 - 98 hours	04 (8)	02 (50)		
Etiology				
Acute symptomatic	34 (68)	04 (11.8)	0.368	> 0.05 (Not significant)
Other etiologies	16 (32)	01 (6.25)		

Note - Figures in parenthesis indicate percentages

In large hospital-based studies, the mortality varies from 3% -50 %, depending on the study design and the case inclusion criteria.[5,10,11] In our study, the mortality was lower (10%), probably due to the fact that the newer definition of SE was used for the case selection and management; unlike the other studies which were done with older definitions. Different clinical studies showed higher mortality amongst the elderly patients; [5,12,13] however, in our study three out of five deaths were between age 51-75 years, and four out of five deaths had occurred in the acute symptomatic group.

In the present study, five (83.3%) out of six non-responders to the AED treatment died had presented after 24 hours. It has been reported in earlier study that the longer the duration of SE, higher is the mortality and that a high degree of mortality is observed in the cases of refractory SE. [14] The statistically significant predictors of mortality in patients with SE were duration of status epilepticus and response to 1st line antiepileptic therapy. Age, gender and etiology of SE were found to be non-significant. Similar findings have also been noted by Murthy *et al*[4], where longer duration of SE, non-responsiveness to 1st line AEDs, acute symptomatic etiology and female sex were associated with poor outcome.

The access to specialist care is a major limiting factor in the developing countries because of the poor health infrastructure and the connectivity, and the delays in transportation. In the present study, those who presented after 24 hours were amongst the non-responder group and they had poor outcomes.

CONCLUSION:

The results of the present study indicate that status epilepticus can occur in epileptic as well as non-epileptic individuals. Intracranial infections are one of the major causes of status epilepticus in developing countries like India. Duration of status epilepticus and non-responsiveness to 1st line antiepileptic treatment are important predictors of a poor outcome.

It is concluded from the results of present study that early recognition of status epilepticus, good knowledge of various etiologies and prompt initiation of therapy and availability of ventilatory facility as well as ICU care is of paramount importance in the management of SE.

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Dental Care: Social Myths and Taboos

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Research Article

ABSTRACT

Dentists have faced many myths and other unproven beliefs which passed from one generation to another. Some of these myths had a significant impact on oral health of the population. Cross sectional questionnaire study was done to ascertain the current prevalence of these cultural taboos and beliefs regarding dentistry among the patients attending the OPD of a dental college. The subjects were recruited from the patients attending the OPD of a dental college and surveyed using a self administered structured questionnaire. Student's t and One-way ANOVA test was employed to find the effect of variables affecting belief of subjects toward oral health. The prevalence of myths about dentistry was high among study population. The deficit was greater in the rural areas. There was statistically significant difference according to age and education.

KEY WORDS: culture, dental beliefs, myths

INTRODUCTION:

Health cannot be isolated from its social context. The social and economic factors have as much influence on health as medical interventions [1]. In old times, well being and disease were deciphered in a cosmological and anthropological viewpoint. Medicine was commanded by supernatural and religious convictions, which were a vital piece of antiquated societies and civilizations [2]. The concept of disease, in which ancient man believed is known as the 'supernatural theory of disease'. Due to the lack of knowledge, the primitive man attributed disease and, in fact, all human sufferings and other calamities to the wrath of Gods, such as the invasion of body by 'evil spirits'[3].

Myths are defined as stories shared by a group of people which are a part of their cultural identity. They have a strong influence in the life of individuals and their way of living including seeking treatment during illness [4]. All people, whether rustic or urban, have their own beliefs and practices concerning well being and disease[5]. This diversity equally applies to oral diseases and treatments. Most of the time people inherit these myths and hand them over to the next generation e.g. small group of people who think that too much brushing can harm the teeth in children, milk teeth don't need care [4].

In Indian viewpoint, a dental myth regularly emerges from conventional belief of non-exploratory base [6]. Communities with inappropriate exposure to oral health care delivery systems are at higher risk of oral diseases, when socio-cultural determinants such as poor living conditions; low education; lack of traditions, beliefs, culture & myths related to oral health are more prevalent[7]. Indian population consists of people from different cultural backgrounds and there is a exceptionally solid impact of the various myths on health seeking behaviour in our population. People believe in spiritual treatment and alternative forms of medicine, as opposed to going to a doctor they visit a hakim (local traditional practitioner).[8] Their thinking is influenced by the prevailing believes about causes of illness and proper methods of cure.[9]

Myths are part and parcel of everyone's lives. Gradually with the development of education, these taboos and beliefs are disappearing, but still they persist and are commonly encountered. Traditional

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Indian beliefs and taboos have been found to correlate inversely with preventive dental health behaviour in the population[10]. Thus the purpose of the present survey was to ascertain the current prevalence of these cultural taboos and beliefs regarding dentistry among the Indian population and to assess the impact of various socio-demographic factors on the prevalence of myths in the study population. The intent is that this assessment will be helpful in shaping the future health programs and creating dental awareness.

MATERIALS AND METHODS:

The present cross-sectional study was carried out for a period of one month in the Department of Public Health Dentistry, People's College of Dental Sciences and Research Centre, Bhopal from 15th July, 2015 to 14th August, 2015. The project was approved by the Institutional ethics committee. Study subjects were recruited from one of satellite centres of department of public health dentistry of a private dental institution in Bhopal city.

A convenient sample of 150 study subjects who visited the satellite centre during the study period and agreed to participate in the study constituted the final sample. The study subjects were assured of the confidentiality of the gathered data. The data was collected using a pre validated, structured, self-administered, close ended questionnaire, consisting of 20 questions seeking information about traditional beliefs, myths and misconceptions regarding oral health and dental care practices[11]. The questionnaire was translated to their local dialect (Hindi) due to colloquial differences between two languages. It was demystified for the convenience of the participants. Three point Likert scale was used to assess the prevalence of myths in dentistry. The questionnaire comprised socio-demographic details of the participants such as their age, gender, education level and employment status, followed by questions regarding common myths and perceptions of participants towards dental treatment, oral health and their oral hygiene practices.

The patients were requested to fill and return the questionnaire then and there itself in order to avoid bias. For illiterate subjects, information was collected through face to face interviews. The collected data was subjected to statistical analysis. SPSS 22.0 was used for statistical analysis. Descriptive statistics were obtained and percentage distributions of responses to questions were calculated. Student's t and One-way ANOVA test were used to determine if there were any associations found between demographics and the myths and perceptions amongst the community. For all tests a p-value of 0.05 or less was used for statistical significance.

RESULTS:

The subjects included in the study comprised of 53% male and 47 % female participants and 74.7% of population belonged to urban population. Each had one or the other myths regarding dentistry. The study population was analyzed based on their age, literacy, level of education and economic status.

38.0% of the study subjects believed that milk teeth need not be cared for because they last only for a few years, and these teeth will anyway be replaced by permanent teeth. 42.7% believe that removal of upper teeth affects vision. With regard to professional cleaning of teeth, 46.7% reported a belief that it causes loosening of teeth and 38.7 % people thought that Keeping tobacco beside a painful tooth reduces tooth pain. On the other hand, 42.32% were aware of root canal treatment as an alternative to extraction. But, lacuna in their information among subjects (42.06%), whether to take dental treatment procedures during pregnancy was observed (Figure 1).

A greater portion of rural people have cultural beliefs and taboos related to dentistry as compared to urban people ($p<0.05$). It was found that education has a significant effect on myths related to dental problems ($p<0.01$) (Table 1). Highly educated patients had lower mean scores regarding cultural beliefs and taboos in dentistry compared to illiterate one. Older age groups have more taboos regarding oral health than younger ones ($p<0.05$) (Table 2).

DISCUSSION:

India is a vast country with varied cultural, socio-economic and geographical background. Every culture has its own particular traditions and convictions some of which have a significant impact on oral health of the population. These social convictions appear to be inflexible as they have a hale affect on the population as the convictions hail from the ancestors. The explanation behind these social convictions and conventional practices are complex and multi-factorial. We tried to focus on the common myths prevalent in Bhopal city. In the present study, the individual who lives in an urban area possesses a higher educational level or who are from younger age groups are significantly more apt to take preventive dental activities paying little mind to social convictions and taboos. These discoveries were like

Table 1: Cultural beliefs and taboos in dentistry among Indian population according to geographic area and Gender.

Groups	Number	Mean	SD	t -value	p -value
Geographical Area					
Urban	112	5.81	3.29	5.26	0.005
Rural	38	9.18	3.74		
Gender					
Male	80	6.75	3.90	0.29	0.094
Female	70	6.57	3.48		

Table 2: Cultural beliefs and taboos in dentistry among Indian population according to education and age group.

Groups	Number	Mean	SD	f-value	p-value
Education					
Illiterate	14	9.78	4.54	4.64	0.004
primary school	16	7.43	2.25		
Higher school	40	6.53	3.42		
Graduate	80	6.03	3.66		
Age group (years)					
18 – 30	54	6.22	3.38	2.80	0.04
30 – 45	43	6.27	3.75		
45 – 60	32	6.87	4.43		
Above 60 years	21	9.13	3.70		

study led by kocher s[12] Chen and Stone[13]. The younger generation had a more positive recognition compared to older population which demonstrates that they are better informed about oral health issues. Likewise, the educated participants responded more positively towards the perception in question compared to un-educated participants. The geriatric populace for the most part acquires solid social and convention convictions, which leaves a lifelong effect on their oral health behaviour. To overcome this problem, education should be provided at all age levels which help in inner cognizance raising, strengthening furthermore modifies unfortunate conduct and practices.

The most widely believed myth was that professional cleaning or scaling loosens the teeth. This kind of misconception is inherited due to false exaggerated information promulgated by those individuals who had past individual negative dental encounters and may be attributed to the way that

numerous individuals have little knowledge about dental treatments. They tend to visit the dental specialist at advanced stages of disease, and around then, if a dentist removes calculus it may be likely that the tooth will become more mobile.[14]

Around a portion of the respondents (44.7%) accept that extraction of upper teeth perniciously influences vision. which was in agreement with that reported by Kumar et al11 kocher et al[12] and nagaraj et al[15] who reported a prevalence of 35.6%, 49.6% and 52% respectively. For instance, extractions performed on older patients, leading to weakening of eye sight because of its vicinity in maxilla are mere coincidental, but still remain a taboo, consequently people relate to this.

The presence of natal teeth was related with supernatural powers, ill-luck and most of them believed that the child would bring misfortune to the family and would become a witch. These kinds of beliefs are considered to be carried out from the ancestors. It was found that still 38.0% of study subjects believe that there is no need to go to dentist until all the permanent teeth of child erupts similar to the result found in some previous studies.[12, 16, 17] They feel that these teeth are going to shed, so treating them as wastes money and time and these teeth will anyway be supplanted by permanent teeth. This is not by any means valid as ahead of schedule loss of milk teeth will meddle with chewing and influence the kid's nourishment; prompts drifting of the adjacent teeth and closure of percentage of the space that is needed for the succeeding permanent teeth to erupt into. Such a loss of space will result in the succedaneous teeth to erupt in unpredictable position resulting in crowding. Therefore milk teeth need to be cared for as much as permanent teeth. So it is appropriate to begin the propensity for cleaning the baby's teeth not long after they erupt in the mouth.

Many subjects believe that root canal treatment as a distinct option for extraction, they have trepidation that it is always painful. The impression of root canals being painful began decades back when root canal treatment was excruciating. Now because of most recent technologies and anaesthetics, root canal treatment today is not any more painful than having a filling of teeth. Indeed, a recent study demonstrated that patients who have encountered root channel treatment are more inclined to depict it as "painless" than patients who have not had root canal treatment [4].

Myths can be prevalent in a population due to a variety of reasons like poor education, cultural beliefs and social misconceptions. They are usually passed on from one generation to the next. It is difficult to break this chain as it is deep seated in the society. It is important to know about these myths and misconceptions prevalent in the population as understanding them is essential to provide good care as well as health education to the people. Based upon the present study, importance should be given for oral health education at individual as well as community level regarding the myths Co-ordinated efforts by dentists, Public Health Specialists, Non Government Organisations (NGO's) and grass root level workers are needed to impart dental health education so that behavioural modification can increase the oral awareness and dental care utilization rate.

CONCLUSION:

The pervasiveness of myths about dentistry was high among study population which could be connected with poor early health seeking behaviour and poor compliance with treatment. Myths and misconceptions associated with dental treatment and custom practices were significantly among uneducated and more seasoned population. The social convictions are because of lack of education and absence of information and they act as hindrances for the utilization of dental service.

LIMITATIONS:

Limitations of the study included that only a convenient sample of study participants who visited our satellite centre which may not be true representatives of the general population for generalizability of results. Future studies are recommended in this direction using a larger, nationwide sample in order to achieve a consistency in the results and people can be aware towards myths regarding dental field.

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Effect of Supplemental Maternal Oxygenation on Placental Blood pH in LSCS under Spinal Anesthesia

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Research Article

ABSTRACT

The use of supplemental oxygen in uncomplicated cesarean deliveries under spinal anesthesia has been thoroughly investigated during recent decades. The aim of this study was to determine whether administering supplemental oxygen via a face mask to the mother is really beneficial or not. Healthy parturients at term undergoing elective cesarean section under spinal anesthesia were randomly allocated into two groups: Group A (n=15), who were allowed to breathe room air and Group O (n=15), who were supplemented with oxygen at the rate of 6liters/min via a face mask. Maternal oxygen saturation was measured continuously by using pulse oximeter. Maternal heart rate and mean arterial pressure were also recorded. Umbilical cord blood samples were collected and sent for arterial blood gas analysis (ABGA) following delivery of the infant. We found out that there was significant fall in pH of the umbilical cord blood in the Group receiving supplemental oxygen. Thus, we conclude that it is unnecessary to routinely supplement oxygen in all healthy parturients undergoing cesarean section under spinal anesthesia.

KEY WORDS: oxygenation, pH, spinal anesthesia

INTRODUCTION:

The use of supplemental oxygen for parturients undergoing cesarean section under spinal anesthesia has been routine practice for more than 30 years.[1] Central neuraxial block may impair functions of respiratory muscles; normally T_4T_5 blockade is given for lower segment section.[2] Many of us administer oxygen to mother thinking it will help the neonate by increasing oxygen delivery to fetus.[3-6] During recent years, it has been observed that the supplementation of oxygen to the mother does not improve fetal oxygenation.[7-8] Recent studies have shown poorer outcome with hyperoxia. It was noted few years ago that administration of 60% oxygen during spinal anesthesia increases free radicals.[9] Reactive oxygen species are formed in the presence of hyperoxia under pHysiological conditions and are generated after hypoxia, ischemia, and reperfusion.[10] They play a key role in mediating tissue injury. Thus, giving oxygen to the mother may benefit the fetus by increasing oxygenation, but also be harmful by accelerating lipid peroxidation. Thus supplementing oxygen to mother may not benefit but may lead to change in acid –base status. We designed the proposed study to observe the effect of maternal oxygenation on neonates.

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MATERIALS AND METHODS:

The study protocol was approved by Institutional ethical committee no DMIMS(DU)/IEC /2014-15/1033. The study design was prospective randomized comparative study. The study included 80 parturients, full term pregnancy posted for elective caesarean section under spinal anesthesia. The patients who had respiratory insufficiency due higher blockade above T_4 or hypotension were excluded from the study. Only the patients who were stable after induction were included in our study. We had selected 30 patients, they were divided in two groups each comprising of 15 patients. Group A (n=15), who breathed room air (not supplemented with oxygen) and group O (n=15), who were supplemented with oxygen at the rate of 6litres/min through mask after induction. The vitals- Heart rate (HR), Mean arterial

pressure (MAP), Arterial saturation (Spo_2) were recorded just after the delivery of baby. After the delivery of the baby and clamping of the umbilical cord, immediately a blood sample was withdrawn from umbilical vein in a heparinized syringe and sent for arterial blood gas analysis (ABG). The collected ABG reports were analyzed with respect to PH and compared statistically. Multiple comparison test-'t test' was used to compare the data statistically.

OBSERVATION:

We observed that in Group A, the mean pH was 7.3413±0.0403 and in group O, the mean pH was 7.2793±0.0369, p value less than 0.0001, statistically significant.

We also observed that there was no significant change in PaO_2 and $PaCO_2$ in both the groups. In group A, mean PaO_2 was 18.54±6.32 and in group O, it was 19.65±5.99. The mean $PaCO_2$ in group A was 52.80±6.32 and in group O it was 49.52±5.76.

We observed that in both the groups there was no difference statistically for heart rate and mean arterial pressure. The average maternal heart rate was 76.67±10.87 in group A, while it was 75.87±9.36 in group O, p value 0.8305 not significant. The mean arterial pressure (MAP) was 75.33±7.17 in Group A, while in Group O, it was 73.04±6.90, p value 0.3714, not significant. The observed SpO2 in group A was 96±1.07%, while in group O it was 99±0.76, p less than 0.0001, highly significant.

RESULTS

A total of 80 parturients were enrolled in the study. Fifty participants were excluded from the study because they had prolonged labor pain, fetal distress and required emergency cesarean section. The mothers' age, body mass index, baseline hematocrit, and indications for cesarean section for the two groups were similar. The surgical details, including uterine incision to delivery interval, duration of surgery, and estimated blood loss were also similar between the groups. In addition, the amount of preload fluid, total intra-operative fluid administration, and vasopressor consumption were not significantly different.

We observed that when oxygen was administered to parturients, there was significant fall in umbilical vein PH which reflects the acid base status of the baby. The mean pH in group A was 7.3413±0.0403, while in group O it was 7.2793±0.0369 as shown in Table 1. In group A mean PaO_2 was 18.54±6.32 and in group O, it was 19.65±5.99. The mean $PaCO_2$ in group A was 52.80±6.32 and in group O, it was 49.52±5.76. There was no significant change in PaO_2 and $PaCO_2$ in both the groups (Table 1).

The mean heart rate in group A was 76.67±10.87 while it was 75.87±9.36 in group O as shown in Table 2. The mean arterial pressure (MAP) was 75.33±7.17 in Group A while in Group O it was 73.04±6.90 as shown in Table 2. The arterial saturation (Spo2) in group A was 96±1.07 % while in group O it was 99±0.76 as shown in Table 2. The pH of both the groups is graphically compared as shown in Graph 1.

DISCUSSION:

Oxygenation during surgical procedure is mandatory now a days but it has it's own side effects.

In 2009, M.Van de Velde says based on current knowledge, to continue supplementing oxygen to mother is not necessary and there is no better outcome for fetus.[11] In 2013,Chatmongkolchart et al studied supplementation of oxygen in caesarean section under regional anesthesia and concluded that it is neither beneficial nor harmful to neonates.[12] In 2014, Arunotai Siriusssawakul and colleagues studied the effect of supplementary oxygen say oxygen supplementation helps when there is desaturation but shall be kept optional.[13]

In our study we observed that supplementing oxygen has no benefits rather it leads to decrease in pH in neonates in patients who were supplemented with oxygen as compared to who were not administered oxygen. Unless the parturients are desaturated, no need to supplement with oxygen routinely.

Table 1:Comparison of arterial blood gas analysis(ABGA) parameters in both the groups.

Parameter	Group A	Group B	*p-value*
pH	7.3413±0.0403	7.2793±0.0369	<0.0001; S
PaO_2	18.54±6.32	19.65±5.99	0.6244; NS
$PaCO_2$	52.80±6.32	49.52±5.76	0.1486; NS

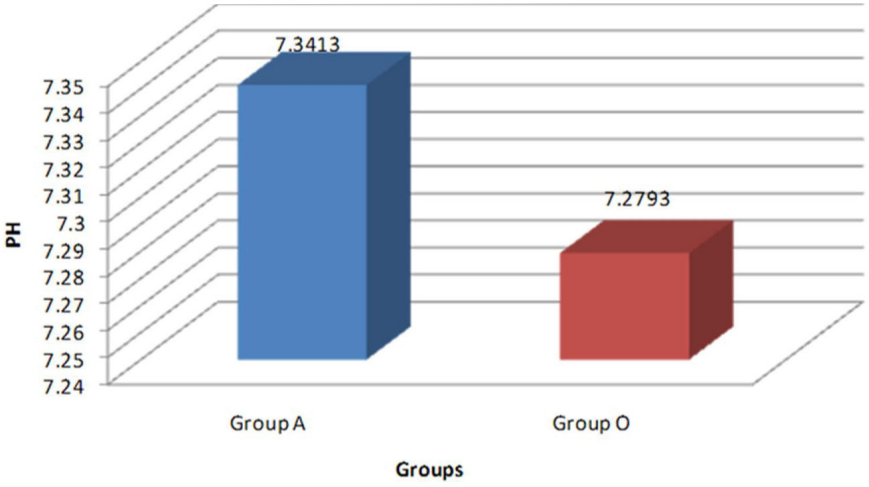
S- Significant; NS- Not significant

Table 2: Comparison of hemodynamic parameters in both the groups.

Parameter	Group A	Group O	*p-value*
Heart rate (mins)	76.67±10.87	75.87±9.36	=0.8305; NS
Mean arterial pressure (mm of Hg)	75.33±7.17	73.04±6.90	= 0.3804; NS
Arterial saturation (Spo_2 %)	96±1.07	99±0.76	<0.0001; S

S- Significant; NS- Not significant

Graph 1: Comparison of pH in both the groups.



CONCLUSION:

It is concluded that routine supplementation of oxygen to healthy parturients undergoing lower segment cesarean section under spinal anesthesia is not necessary as it does not improve fetal oxygenation rather it may be harmful to the baby as it leads to acidosis and may cause formation of free radicals, which are harmful.

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Research Article

Impact of Training on ASHAs in Selected Districts of Madhya Pradesh

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ABSTRACT

A cross sectional study amongst ASHAs (Accredited Social Health Activists) working under National Rural Health Mission (NRHM) was conducted in randomly selected two districts each from Indore and Ujjain divisions of the state of Madhya Pradesh. Data was collected with the help of Pre & Post-test evaluation of trainees, feedback from trainees, passive observation of training centers, and interview of trainees by using semi structured questionnaire. Work experience of ASHAs in Ujjain Division was less than 5 years amongst almost 76% as compare to Indore division where it was 53% only. In Ujjain division 150 (31. 91 %) ASHAs were not trained in first four modules of ASHA training as compared to 12.15 % (62) ASHA from Indore division. The satisfaction level between Indore and Ujjain divisions were different with a higher satisfaction level in Indore division as compared to Ujjain division ASHAs. p value< 0.05. Complete training and infrastructure had significant impact on knowledge of ASHAs about the new born health care e.g. Breast feeding, fever, hypothermia, malnutrition and danger signs as well as other indicators amongst sick children.

KEY WORDS: accredited social health activists (ASHA),impact, training

INTRODUCTION:

Developing countries especially India has seen so many ups and down particularly in health sectors before and after Independence. Many health programs in health sectors have failed in the past or could not achieve desired objectives. Therefore recognizing the importance of Health in the process of economic and social development and improving the quality of life of our citizens, a paradigm shift took place in India and the Government of Indiadecided to launch a National Rural Health Mission (NRHM) to address the health needs of rural population, especially the vulnerable sections of society. Hence to overcome this situation a new band of community based functionaries, named as Accredited Social Health Activist (ASHA), is functional to fill this void.

The National Rural Health Mission (NRHM) launched in April, 2005 has completed seven years of implementation and is now commencing its second phase. The ASHA programme was introduced as a key component of the community processes intervention. Over the seven year period, the ASHA programme has emerged as the largest community health worker programme in the world, and is considered a critical contributor to enabling people's participation in health[1,2,3]

ASHA (Accredited Social Health Activist) is a health activist in the community who creates awareness on health and its social determinants and mobilize the community towards local health planning and increased utilization and accountability of the existing health services[4]. They act as a 'bridge' between the rural people and health service outlets and would play a central role, in achieving national health and population policy goals[5,6]. The effectiveness of ASHA worker largely depends on the training and support from both the health system and the community[7].

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MATERIALS AND METHODS:

It was a cross sectional study. The study sites

included: randomly selected two districts each from Indore and Ujjain divisions of the state of Madhya Pradesh namely Indore, Jhabua and Dewas Neemuch; and the ASHA training centers run by NGOs in each district namely, Training center Jeevan Jyoti Prashikshan Kendra, labor colony Rau, main AB road run by NGO Bhartiya Gramin Mahila Sangh (BGMS) Indore; Training center ASRA, 26, Badridham Nagar Dewas (M.P.) run by NGO Asra Samajik Lok Kalian Samiti Dewas; Training center Kaku Residency Ranapur Road in front of PG College, Jhabua run by NGO Ambika Shiksha Sansthan Kalyan Samiti, Bhopa and Training center Maheshwari Bhavan, Neemuch by NGO kailash Boriwal Sahaj Samaj Utthan Samiti, 7 Parda complex, Near Central bank, kamal Chowk, Neemuch. The Study Population was: 980 ASHAs after their skill based training (6th & 7th modules) at their District training Centre. The study was conducted for a period of 24 Months (i.e. from January 2013 to December 2014).The study subjects were: ASHAs (Accredited Social Health Activists).The study tools included: Pre & Post-test questionnaire for trainees, Feedback form for trainees, Observation checklist for assessment of infrastructure, staff, teaching aids and other facility at training centers.No violation of ethic was visible as the study was enquiry driven and non-interventional in nature.The questionnaires were redesigned & validated (pretested) in study areas with an appropriate small sample size of ASHAs. The data collected were analyzed through percentages and frequencies in which the data were presented in table formats, pie charts and histograms which were obtained using Excel and using SPSS (Statistical Package for Social Science).

RESULTS:

Training plan and process at all four training centers was almost similar. Since ASHA training had to go a long way(several months) as each ASHA of the respective district had to be trained, the plan for training was made well in advance for all ASHAs divided in several batches, each batch with 22 to 30 ASHAs .

There were lack of facilities at Dewas district training center of Ujjain division. It did not have connectivity & accessibility, separate dormitories and mess for residing trainees instead the lecture halls itself were utilized as hostels in the non-training hours and in the night. The toilets/ bathroom were attached to lecture halls itself and no other separate toilet facility was available. A small dining hall was available which was reserved only for trainers.

There was no facility of library, health clinic and outdoor space for recreation and facility of crèche at most of the training center.

Participants come by their own convenience to the training center. Training was conducted as per the schedule issued by state govt. The training schedule was of five continuous days, the 4th day of which was fixed for field training and 5th day for evaluation/ theory and practical exams. Accommodation and food facility was provided free of cost (govt. fund) to the trainees and trainers. After the training hours, the trainees were left for recreational activities and group discussions. Two trainers stay at the training center in night to keep vigil over the trainees and help them whenever required. The Cheques of TA/DA were distributed to each participant on the last day of training before the trainees leave from training center.

Out of 980 ASHAs included in the study almost 93% were married and remaining 7% were unmarried/ widowed. The mean age of ASHAs was 26.5 years with a range of 17 to 58 years in both the divisions. About 3/4th (72%) of ASHAs had eligible qualification of class 8th and above while the rest (28%) were not eligible, and selected due to unavailability of qualified candidates. Out of total 510 ASHAs in Indore division 160(16.32%)and in Ujjain division it was 114 out of 470 (11.63%)of ASHAs who did not have the minimum qualification (class 8th pass) required to be selected as ASHA. Almost more than 40% of the ASHAs had working experience of less than 5 year. Average Monthly Household Income (in Rs.) was also very less and it was more in districts Ujjain division (4896/-Rs) as compare to Indore division (2960/-Rs).

In Ujjain division 150 ASHA (31. 91 %) ASHAs were not trained in first four modules of ASHA training as compare to 12.15 % (62) ASHA from Indore division.

The satisfaction regarding completion of training objectives were compared for Indore and Ujjain Divisions.The satisfaction level between Indore and Ujjain divisions were different with a higher satisfaction level in Indore division as compared to Ujjain division ASHAs. p value< 0.05.

DISCUSSION:

Government through NRHM is making lots of effort to strengthen the ASHA programme by selection and training process. This study has been conducted to know the effect of training (presently skill based

Table 1: Facilities available at different District training centers.

S. No.	Facilities	Indore		Ujjain Division	
		Indore	Jhabua	Dewas	Neemuch
1	Building	Pucca	Pucca	Pucca	Pucca
2	Connectivity & accessibility	Yes	Yes	No	Yes
3	Lectures halls (adequate capacity)	Yes	Yes	Yes	Yes
4	Light &ventilation of halls	Normal	Normal	Normal	Normal
5	AV aids, black/white board , LCD	Yes	Yes	Yes	Yes
6	Separate hostel facility	Yes	Yes	No	Yes
7	Dining hall and mess	Yes	No	No	Yes
8	Sufficient indoor &outdoor space	Yes	No	No	No
9	Separate toilet facility	Yes	Yes	No	Yes
10	Safe Drinking water	Yes	Yes	Yes	Yes
11	Health care facility / clinic	Yes	Yes	No	Yes
12	Library	Yes	No	No	Yes
13	Crèche facility/children park	No	No	No	No
14	Notice board	No	No	No	Yes

Table 2: Observation of the trainings:

S. No.	Key findings	Indore Division		Ujjain Division	
		Indore	Jhabua	Dewas	Neemuch
1	Inauguration session as per schedule	No	No	No	No
2	All the participants come before the start of training session	No	No	No	No
3	Registration of the participants	Yes	Yes	Yes	Yes
4	Distribution of training kit and stationary to the ASHAs	Yes	Yes	Yes	Yes
5	Batch size limited to 30 participants	Yes	Yes	Yes	Yes
6	Formal introduction and recap of the previous training session	Yes	Yes	Yes	Yes
7	Trainers stick to the topics as per schedule	Yes	Yes	Yes	Yes
8	Cross questioning from participants and explanation by trainers	Yes	Yes	Yes	Yes
9	Orientation of all the participants throughout the lecture	No	No	No	No
10	Availability charts, models, dummies etc	Yes	Yes	Yes	Yes
11	Daily Assignments to the trainees	Yes	Yes	Yes	Yes
12	All participants go to field visits	Yes	Yes	Yes	Yes
13	All participants go through theory and practical exams	Yes	Yes	Yes	Yes
14	Got the remunerations/TA /DA for training	Yes	Yes	Yes	Yes

Table 3: Study Sample demographic Profile of ASHAs in the selected districts:

S. No.	Characters	Indore Division		Total	Ujjain Division		Total
		Indore	Jhabua		Dewas	Neemuch	
1	No. of ASHAs Surveyed	270 (27.55%)	240 (24.4%)	510 (52.04%)	310 (31.63%)	160 (16.32%)	470 (47.95%)
2	Average Age of ASHAS (in years)	27	26	26.5 Average	28	25	26.5 Average
3	Average no. of Married ASHAs	252 (93.33%)	239 (99.5%)	491 (96.30%)	284 (92%)	133 (83.2%)	417 (87.5.5%)
4	% Educated below 8th Grade	28% (76)	35% (84)	16.32% (160)	24% (74)	25% (40)	11.63% (114)
5	Average Monthly Household Income (in Rs.)	3665	2255	2960/ -	4192	5600	4896/ -
6	Average No. of Years of Service	05.60	3.5	04.55	04.03	05.00	4.51

Table 4: Training status (prior training of first four modules).

S. No	Status	Indore	Jhabua	Total (%)	Dewas	Neemuch	Total (%)
1.	Trained in 1 -4 modules	241	207	448 (87.84%)	189	131	320 (68.08%)
2.	Not trained in 1 - 4 modules	29	33	62 (12.15%)	121	29	150 (31.91)
	Total	270	240	510	310	160	470 (100%)

Table 5: Comparison of Indore and Ujjain Division for satisfaction regarding completion of training objectives:

Two sample proportion	Indore Division (Total -510)	Ujjain Division (Total -470)		
Objectives:	Satisfied	Satisfied	z score	p value
To take care of the new-born, support and help the mother to breastfeed, and to keep the baby warm.	450	305	8.90	0.0001
Counsel mother for breastfeeding and Emphasize importance of early and exclusive breastfeeding	425	290	7.77	0.0001
Identify the new-born with fever and hypothermia and Teach mothers how to keep the new-born warm	415	296	6.53	0.0001
Communicate essential messages for prevention of malnutrition, advice on feeding and on prevention of illness, and on access to health and nutrition services	475	345	8.49	0.0001
Identify general danger signs among sick children, recognize symptoms of common illnesses and Enable prompt referral.	468	365	6.20	0.0001

training, 6th& 7th module) on ASHAs knowledge, skills and their work behavior.

Currently second round of skill based training (6th and 7th module) is in process in most of the districts of Madhya Pradesh including Indore Jhabua, Dewas and Neemuch. This is a five days residential training being organized only at district headquarters of each district by selected non-governmental organization for each district.

Training centers at all the four districts had micro plan issued by government and a written schedule for training. All the centers followed the training plan and schedule but there was delay in the start-up of session on the first day of training. It was found that most of ASHAs came late at the training center on first day instead of a day before in the evening as per guidelines.

After training center evaluation, different components eg.reaction, learning /knowledge were evaluated on 980 ASHAs, 270 from Indore, 310 from Dewas, 240 from Jhabua and 160 from Neemuch. The average age of ASHAs was around 26.5 years in both the divisions whichis lower compared to study done by Bajpayi N. et al (2010)[8] in Bihar (31years), Uttar Pradesh (31years), Rajasthan (33 years) and Chhattisgarh (32). However it was similar to the study by Srivastav DK et al(2009)[9] in which more than half of the ASHAs were in age group 20-29 years. It is also lower compared to study done by Abel M et al, 29.8[2] years. 26.5% of ASHAs were below the minimum age criteria i.e. less 25 years of age, recruited due to unavailability of other candidate.

More than one third, 160 (31.50%) ASHAs had less than essential qualification (class 8th) i.e. was below class 8th pass.The proportion is similar to the study done by Bajpayi N. et al[8] in 2010 where 28% of the ASHAs from Chhattisgarh were below class 8th standard. A study by Bhatt H, et al[10] in Uttarakhand in 2012 also revealed that most of the ASHAs were qualified 8th and above and only few were qualified below 8th.

The reaction or feedback indicated that satisfaction level between Indore and Ujjain divisions were different with a higher satisfaction level in Indore division (85%), as compared to ASHAs of Ujjain division (68%), with objectives i.e. know how to perform different activities for new born care, care of sick child, counsel mothers for baby feeding, prevent new born from hypothermia and educate mothers for prevention of child malnutrition.

The reaction was similar as in study by Bhatt H, et al[10] in Uttarakhand in year 2012, where most of the ASHAs admit that the training is beneficial, but nearly half of them don't consider the training to be adequate. Also in study by Bajpayi N. et al[8] in 2010 most of the trainees were satisfied with training activity and those who were not satisfied wanted a repeat training. 49% of the ASHAs from Dewas and Jhabua complained of inadequate facility for residential training, space and bathroom /toilet facility. There was no facility of library, health clinic and outdoor space for recreation and facility of crèche at all the training center.

Most of the participants have adequate knowledge about the new born care and danger signs etc.The result was similar to study by Mahyavanshi DK, et al, 2011[11] in which around 90% of ASHAs had poor knowledge regarding hypothermia and kangaroo mother care, 80% had poor knowledge regarding neonatal infection and 86.16% of ASHA workers had poor knowledge regarding referral condition and when and where to refer the baby. Also around 70% had poor knowledge regarding correct breast feeding practices, and nearly 86% and 71% had poor knowledge of problems regarding breast feeding and complimentary feeding respectively.In another study by Srivastav SR, et al, 2012[12] evaluated the knowledge of trained ASHAs about child Health care in which 15-20% of ASHAs were not aware of the danger signals of dehydration, 20-30% were unaware of danger symptoms/ signs of pneumonia in spite of undergoing training. Around 30-40% of ASHAs were not aware of the dangerous AEFI (after effects following immunization).

CONCLUSION:

Training had significant impact on knowledge of ASHAs about the new born health care eg. Breastfeeding, fever and hypothermia, malnutrition and danger signs among sick children. Those who are trained gave satisfactory response regarding completion of training objectives. So complete training of all the modules is most important and required process of knowledge improvement of ASHAs which is evident from low level of satisfaction in Ujjain division where more than 1/3rd were not trained in module 1-4 and had significant lack of training facilities.

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Research Article

Renal Dysfunction in Perinatal Asphyxia & its Correlation with Apgar Score and Hypoxic Ischemic Encephalopathy Stage

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ABSTRACT

Renal involvement is frequent in perinatal asphyxia. The severity of renal involvement and adverse outcome are correlated with severity of asphyxia and HIE stage. The study determined the incidence of renal failure after perinatal asphyxia, to assess comprehensively the renal functions of asphyxiated newborns and to correlate severity and type of renal failure with Apgar Score and HIE stage. This prospective cohort study was conducted on total 50 newborns of >34wks gestational age .All neonates were evaluated clinically and their renal functions were assessed on day 3 and 5. Assessment of fractional excretion of sodium (FeNa) was done to know the type of renal failure. Criteria for labeling an asphyxiated neonate as having renal failure were serum creatinine >1.5mg/dl or oliguria<0.5ml/kg/hr for >6hrs beyond first day of life.HIE staging was done by Sarnat and Sarnat staging system. Results were tabulated and analyzed statistically by student t test , Chi-Square test and Anova test. Acute renal failure was common among asphyxiated newborns with incidence of 57.5%.in our study. Incidence of renal failure increases as Apgar score decreases and as HIE stage progresses. Blood urea and serum creatinine were significantly higher in asphyxiated babies, compared to control group (p value <0.001) .Biochemical derangements correlated well with HIE staging and Apgar score and this difference was found significant (p value<0.05).Oliguric renal failure was present in 35% of asphyxiated babies. Incidence of intrinsic renal failure (FeNa>2.5) was more in severely asphyxiated and HIE stage-III babies. Predictors of adverse outcome are intrinsic renal failure, higher HIE stage and severe asphyxia.

KEY WORDS: ARF (acute renal failure), FeNa (fractional excretion of sodium), HIE (hypoxic ischemic encephalopathy), perinatal asphyxia, intrinsic renal failure

INTRODUCTION:

Perinatal asphyxia is one of the most common cause of neonatal mortality and morbidity in developing countries. Hypoxia and ischemia can damage almost every tissue and organ of body, and kidney involvement is seen in about 50%-72% of cases. Milder episodes of ischemia may cause reversible tubular changes, seen microscopically. More severe injury involves the glomerulus and entire nephron may be involved due to corticomedullary necrosis as a result of infarction. This study was performed to determine the incidence of renal failure in perinatal asphyxia, to assess comprehensively the renal function in asphyxiated babies and to correlate the severity and type of renal failure with Apgar score (6) and encephalopathy(HIE) staging of asphyxiated neonates.

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MATERIALS AND METHODS:

The study design was prospective cohort study. This study was conducted on total 50 newborns of ≥ 34wks gestational age, admitted in Neonatology, Department of Pediatrics, M. L. B. Medical College, Jhansi, from January 2009 to June 2010. The study group comprised of 40 neonates, with gestational age ≥ 34 weeks, born by LSCS or normal vaginal delivery and who were appropriate for their gestational age. Babies with Apgar score of 6 or less at 1min or babies who needed resuscitation for ≥ 5min, were included in study group.

Control group comprised of 10 gestation and weight matched babies, who had no asphyxia (1 min Apgar score ≥7).The number of control group was limited for ethical reasons. Babies with major congenital malformation, Septicemia, history of leaking per vaginum for > 12 hrs in mothers, babies of mothers with any medical problem in antenatal period were excluded from study.

All the neonates were evaluated clinically and their renal functions were assessed on 3rd and 5th day. Renal profile was done by estimation of serum creatinine , urea, sodium and potassium on day 3rd and day 5th. Microscopic urine analysis, estimation of urine for protein, sugar, specific gravity and estimation of urine creatinine and sodium were also done. Assessment of fractional excretion of sodium was done to know the type of renal failure. Criteria adopted for labeling an asphyxiated neonate as having renal failure were serum creatinine >1.5 mg/dl (>133 micromol / lit) on 3rd day of life or Urine output < 0.5 ml / kg / hr for >6 hrs beyond 24 hrs of life[3,4]. In microscopic urine analysis, presence of granular cast, hyaline cast, RBC>5/hpf, protein(>1+) and tubular cells suggest an intrinsic cause.

Severity of asphyxia was determined by Apgar score (moderate asphyxia is slow gasping breathing or Apgar score of 4-6 at 1 minute of age and severe asphyxia is no breathing or Apgar score of 0 -3 at 1minute of age),(NNPD-2000). HIE staging was done by Sarnat and Sarnat scoring system (1976)[7]. FeNa (fractional excretion of sodium) >2.5% was considered as an indicator of intrinsic renal failure.

$$\text{Fractional Excretion of Na} = \frac{\text{Urinary Na} \times \text{Plasma Creatinine}}{\text{Plasma Na} \times \text{Urinary Creatinine}}$$

Proper history with special emphasis on antenatal, natal and postnatal history, cry status, details of resuscitation were also recorded. Thorough clinical examination were done, special emphasis in neurological examination was given in assessment of HIE stage of baby like level of consciousness, tone, posture, convulsion, pupil and neonatal reflexes. Gestational age assessment was done by LMP and New Ballard scoring system. Blood sampling was done from a peripheral vein. Laboratory method applied for creatinine estimation was modified alkaline picrate method. Urea estimation was done by di-acetyl amino oxide method by kit. Sodium and potassium was measured on sodium and potassium analyzer. Estimation of urine for specific gravity, sugar, protein and ketones was done by dipstick colour strips for urine analysis. Microscopic examination of urine was done to see haematuria (5RBC/hpf). Statistical analysis was performed by using unpaired student 't' test, chi-square test and 'Anova' test by using SPSS software-17.0.

RESULTS:

Cases of perinatal asphyxia with renal failure were kept in group Ia and without renal failure were kept in group Ib. Control group were kept in group-II. In this study, incidence of moderate asphyxia was 30% and that of severe asphyxia was 70%. Incidence of ARF (Acute Renal Failure) in asphyxiated babies was 57.5%. There was a significant correlation (p value < 0.001) between study and control group when blood urea and serum creatinine values were compared . This showed that asphyxiated babies had deranged renal functions as compared to non-asphyxiated babies.

Incidence of ARF in HIE was 26.7% in stage I,70% in stage II and 100% in stage III. This showed that as HIE stage progressed, more renal dysfunction was seen in asphyxiated babies.This difference in incidence was found statistically significant (p value<0.05 done by Chi-square test). Likewise, incidence of renal failure in moderate asphyxia was 33.33% whereas in severe asphyxia was 67.8%. This difference in incidence was also statistically significant (p value<0.05 done by Chi-square test). Thus renal failure increases as apgar score decreases.

Serum sodium level was almost unaffected in study and control group except for a slightly lower level in ARF cases. (Serum sodium level was 132.04± 2.36 and 131±1.65 on 3rd and 5th day respectively in ARF cases, while 135.41±2.15 and 136.64±1.72 on 3rd and 5th day respectively in non-ARF cases. Serum potassium level in asphyxiated ARF babies was found to be higher (5.8±0.36 on 3rd day and 6.2±0.43 on 5th day) than non-ARF asphyxiated babies (4.5±0.4 on 3rd day and 4.4±0.23 on 5th day respectively). Thus incidence of hyperkalemia (K > 6meq/lit) in ARF cases was 39.13%.Incidence of haematuria in ARF cases was 30%, most of them were of intrinsic renal failure type. Frequency of proteinuria (protein > 1+) in this study was 47.82%. Incidence of pre-renal renal failure was 60.9% while of intrinsic renal failure was 39.1%.

High FeNa is more specific for intrinsic renal tubular damage. Oliguric renal failure was present in 35% of cases and non-oliguric renal failure was present in 65% of cases of renal failure.

Table 1: Biochemical parameters in moderate and severe asphyxia (according to apgar score)

	Blood urea (mean SD)	Moderate vs severe asphyxia (p value)	Serum creatinine (mean SD)	Moderate vs severe asphyxia (p value)
Moderate asphyxia (n=12) (Apgar 4-6)	29.6±18.3	0.02	1.18±0.374	0.003
Severe asphyxia (n=28) (Apgar ≤3)	48.4±24.1		1.66±0.462	

Table 2: Co-relation of severity of asphyxia and type of renal failure.

Type of asphyxia	pre-renal ARF		Intrinsic ARF	
	No. of cases	%	No. of cases	%
Moderate asphyxia (n=4)	2	50	2	50
Severe asphyxia (n=19)	7	36.85	12	63.15

Table 3: Urea and creatinine levels correlated with HIE Staging.

HIE staging of group I (Study group)	n	Blood urea (mg/dl) in group I Mean SD	p-value (between stage I,II,III by Anova test)	Serum creatinine (mg/dl) in group I Mean SD	p-value (between stage I,II,III by Anova test)
I	15	28.5±20.3		1.11±0.358	
II	20	47±20.2	p-value <0.005	1.65±0.353	p-value <0.005
III	5	68.4±23.2		2.18±0.36	
Total	40	42.8±23.9		1.52±0.486	

The severity of asphyxia (judged by Apgar score) was correlated with biochemical parameters (blood urea and serum creatinine) and this association was found significant (p value < 0.05),by student t test (Table 1). As severity of asphyxia increased, more cases were found to had intrinsic renal failure (% of intrinsic renal failure in moderate asphyxia was 50% and in severe asphyxia was 63.15%), (Table 2). Thus severely asphyxiated babies were more likely to have intrinsic renal failure. Survival rate in moderate asphyxia was 100%, while in severe asphyxia was 57.24%.

As HIE stage progressed, biochemical parameters (blood urea and serum creatinine) showed statistically significant difference when cases in HIE stage-I,II and III were compared by Anova test, all values showed significant difference, p value < 0.005 (Table 3).

As HIE stage progressed, more babies developed intrinsic type of renal failure, as in HIE stage-I and II, 50% were having intrinsic renal failure ,while in HIE- III, this figure was 100% . Mortality was also found to increase when HIE stage progressed, as survival is 100% in stage I, 65% in stage II & 0% in stage III.

Of all ARF cases,35% babies developed oliguric renal failure (urine output <0.5ml/kg/hr) and 65% had non oliguric renal failure (urine output >0.5/kg/hr).

DISCUSSION:

Perinatal asphyxia is a major cause of neonatal morbidity and mortality, and kidney is very sensitive to oxygen deprivation, occurring as a result of perinatal asphyxia. Within 24 hrs of an ischemic

episode, renal insufficiency and acute renal tubular necrosis may occur and if left untreated, irreversible cortical or medullary necrosis may develop[8].

The definition of perinatal asphyxia was chosen as 1 min apgar score 6 and or need for resuscitation 5 min because need for positive pressure ventilation 5min corresponds to cord pH 7, which is one of the reliable marker of birth asphyxia[2].

In this study, incidence of acute renal failure was 57.5% in asphyxiated babies. This is well matched with earlier studies of chevalier (1984), Perlman (1989), Jayshree (1991) and Nouri(2008)[9,10,5,11].

Hyperkalemia was found in 39.13% of ARF cases. This is also comparable to previous studies. Low GFR in prerenal failure and hypoxic tubular injury in intrinsic renal failure are thus responsible for this hyperkalemia in ARF cases.

30% of babies with ARF developed haematuria and most of them were of intrinsic renal failure type, while 47.82% of babies developed proteinuria (> 1+ protein / HPF) and majority of them were of intrinsic renal failure type. Both of them are related to acute tubular injury[10].

Incidence of oliguric renal failure was 35% of ARF cases. Oliguria , as reported by other authors, ranged from 25% to 69.3% (12,1).Renal parenchymal injury in non-oliguric as well as oliguric renal failure is essentially similar but heterogeneous response of individual nephron and variable damage to tubular epithelium results in anatomical damage in majority of nephrons leading to reduction in single nephron GFR and decreased tubular fluid flow. But if damage to tubular epithelium is less severe, there occurs decrease in fractional reabsorption, which excess the decrease in single nephron GFR leading to polyuria in non oliguric renal failure[2].

In this study, both HIE stage and severity of asphyxia (judged by Apgar score), were correlated with blood urea and serum creatinine and this correlation was found statistically significant (p value < 0.05). As severity of asphyxia increased and HIE stage progressed from stage-I to stage-III, higher values of blood urea and serum creatinine were observed, more number of intrinsic renal failure cases were found and more mortality was observed. Thus renal function assessment using blood urea and serum creatinine seems to be correlated with neurological involvement and degree of asphyxia.

Besides HIE-stage-III & severe asphyxia (as judged by Apgar score), intrinsic renal failure and oliguria are also a predictor of poor outcome. FeNa is an early indicator of tubular dysfunction which differentiates prerenal from intrinsic renal failure. Though from earlier studies, high serum creatinine and high blood urea had 100% sensitivity & negative predictive value to predict adverse outcome[4], these parameter are however poor predictors of adverse outcomes when compared to clinical marker like Apgar score 3 and HIE stage II/III.

Early detection of renal dysfunction in asphyxiated babies can help to prepare guidelines for management of these patients. An early intervention can prevent intrinsic renal failure and thus improve survival of these babies. Lastly the best approach to reduce mortality due to renal failure in asphyxiated neonate is to identify high risk cases for perinatal asphyxia in antepartum and intrapartum stage itself, and prevent this unfortunate event.

CONCLUSIONS:

Transient renal failure is commonly observed in perinatal asphyxia but if hypoxic insults are prolonged, it may lead to irreversible cortical necrosis. Renal function assessment using blood urea and plasma creatinine level is corrected with HIE stage and degree of asphyxia and as HIE stage progresses, more renal dysfunction is observed. Mortality was higher in babies with oliguric renal failure. FeNa is an early indicator of tubular dysfunction which differentiates pre-renal from intrinsic renal failure. Early detection of renal dysfunction in asphyxiated neonates can help to prepare guidelines for management of these patients. An early intervention can prevent intrinsic renal failure and thus improve the survival of these neonates.

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Case Report

Unhealed Chin Wound in an Infant with Leukocyte Adhesion Deficiency Type-I

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ABSTRACT

Leukocyte adhesion deficiency type1(LAD-1) is a rare, autosomal recessive disorder in which phagocyte adhesion, chemotaxis and ingestion of C3 biopsonised microbes are impaired owing to mutations in the gene for CD18β sub unit of β2 integrin. We report a 38 day old male infant with LAD-1 and infected unhealed chin wound and history of delayed umbilical cord separation. It is highly recommended that patients who diagnosed with mild to moderate LAD-I with recurrent skin infections and simultaneous weak responses to conventional therapy to undergo bone marrow transplantation (BMT) to prohibit subsequent life-threatening complications.

KEY WORDS: leukocyte adhesion deficiency type-1; primary immunodeficiency disorder; unhealed wound

INTRODUCTION:

Leukocyte adhesion deficiency type-1 (LAD-1) is a rare disease with only 200 cases reported in the medical literature.[1] LAD-1 was first described as a separate entity among immunodeficiencies in 1979 by Hayward et al.[2] LAD-1 is a rare, inherited immunodeficiency that affects one per million people yearly and usually presents with recurrent, indolent bacterial infections of the skin, mouth, and respiratory tract with impaired pus formation and wound healing.[3] Patarroyo M, Makgoba M.[4] stated that Leucocyte adhesion deficiency is characterized by the inability of leucocytes, especially neutrophils, to emigrate from the blood stream towards sites of inflammation. Infectious foci are therefore non-purulent and eventually become necrotic because of abnormal wound healing. The genetic defect in LAD-1 has been mapped to mutations of the gene encoding for CD18 on chromosome 2Iq22.3. The clinical picture is characterized by delayed umbilical cord separation, recurrent life threatening bacterial infection of skin and mucous membrane, impaired pus formation, delayed wound healing and persistent neutrophilia. Early studies[5] found that leukocytes from patients with LAD-1 were deficient in the expression of the three integrins containing beta 2 or CD18 (Mac-1, LFA 1, p150, 95). Paucity or absence of CD11/CD18 neutrophils by flow cytometry is diagnostic. If less than 1% of neutrophils have CD11/CD18 markers, the prognosis is poor; the average life span is 10 years. The only known therapy is bone marrow transplantation. [6] Correct and early diagnosis of LAD-1 is vital to the success of treatment and prevention of aggressive infections; early diagnostic suspicion and early treatment improve the prognosis.[7]

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CASE REPORT:

A 38-day old Saudi infant of un-consanguineous parents, product of full term pregnancy with normal delivery and birth weight of 2.8 kg, had received BCG and Hepatitis B vaccine at birth and he was discharged home in good condition. He was well till one week prior to admission; then he started to develop history of fever for one week followed by ulcerative lesion on his chin. Fever was on and off, high grade which reached 38.9.1°C, responding partially to antipyretics, not associated

with chills or sweating. On the sixth day of fever, he developed ulcerative lesion on his chin about 0.5 cm below the lower lip which was single, rounded in shape and 1 cm in diameter, progressive with time in size and crusted. No history of mouth ulcers, oral thrush, skin rash or same lesion on other parts of the body. No history of poor feeding or lethargy. No history of cough, shortness of breath, ear discharge, abdominal distension, vomiting, diarrhea, change in color or odor of urine or joint swelling. No history of trauma, insect bites, traveling to endemic area or contact with sick patient. Systemic review was unremarkable apart from delayed umbilical cord separation; it was at age of 30 day old. He has three healthy siblings (one brother and two sisters). There was no history of same illness in the family.

On examination, patient was conscious, alert with normal body built. He was not on reparatory distress, not cyanosed, pale or jaundiced with no apparent dysmorphic features. BCG scar was present. Vital Signs: Temperature 38.6°C, BP: 91/62 mmHg, RR: 36 breath/min and pulse: 140 beat/min. Growth parameter: weight: 4.5 Kg, height: 53 cm and head circumference: 35cm (All growth parameters were on 50 percentiles for his age). There was well defined ulcerative lesion on the chin 0.5 cm below the lower lip which was single, rounded in shape about 1.0 to 1.0 cm in size, progressive with time in size and erythematic with central crustation (Figure1). Systemic examination was unremarkable.

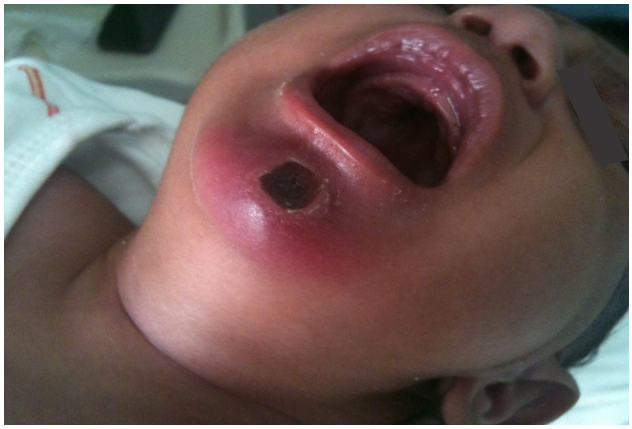

Figure 1: An image showed a well-defined non suppurative erythematic ulcerative lesion with central crustation on the chin 0.5 cm below the lower lip which was single, rounded in shape about 1.0 to 1.0 cm in size with redness around it.

LABORATORY WORKUP:

Complete blood count: WBC: 98000, RBC: 4.60, HGB 12 g/dl, HCT 42, MCV 89 , MCH 29, PLT 436, NEUT : 82,6%, LYMPH:8,2%, MONO: 8,6%, ESO: 0 ,2%, BASO: 0,4%. Peripheral blood smear showed: Neutrophi count of 44.600, shift to left with normochromic normocytic anemia with leukocytosis and absolute neutrophilia. WBC 98,2 dropped down to 68000 after 2 days and then to 49000 in the 4th day of admission. ESR:45 MM/hr, Renal and hepatic function tests were preserved. Blood culture: Staphlococcus Hominis. Urine and stool cultures were negative. Cerebrospinal fluid (CSF) was normal with negative culture. CD 18 and CD 11 were low.

The diagnosis of LAD-1 with leukocytosis and septicemia was made. Patient was admitted to pediatric medical ward and treated with antibiotics; repeated blood culture came negative and was referred to higher center for stem cell transplant. Patient underwent a successful allogeneic stem cell transplant from fully-matched mother at age of 4 month of age at King Faisal Specialist Hospital and Research Center in Riyadh. The lesion on the chin was improved. The patient had a follow up in the clinic in our hospital; he was fine with no chin wound and no complaint.

DISCUSSION:

Leukocyte adhesion deficiency type-1 (LAD-1) is a rare disease with only 200 cases reported in the medical literature.[1] LAD-1 was first described as a separate entity among immunodeficiencies in 1979 by Hayward et al.[2] LAD-1 is a rare, inherited immunodeficiency that affects one per million people yearly and usually presents with recurrent, indolent bacterial infections of the skin, mouth, and respiratory tract with impaired pus formation and wound healing.[3] Patarroyo M, MakgobaM.[4] stated that Leucocyte adhesion deficiency is characterized by the inability of leucocytes, especially neutrophils, to emigrate from the blood stream towards sites of inflammation. Infectious foci are therefore non-purulent and eventually become necrotic because of abnormal wound healing. The genetic defect in LAD-1 has been mapped to mutations of the gene encoding for CD18 on chromosome 2Iq22.3. The clinical picture is characterized by delayed umbilical cord separation, recurrent life threatening bacterial infection of skin and mucous membrane, impaired pus formation, delayed wound healing and persistent neutrophilia. Early studies[5] found that leukocytes from patients with LAD-1 were deficient in the expression of the three integrins containing beta 2 or CD18 (Mac-1, LFA 1, p150, 95). Paucity or absence of CD11/CD18 neutrophils by flow cytometry is diagnostic. If less than 1% of neutrophils have CD11/CD18 markers, the prognosis is poor; the]

average life span is 10 years. The only known therapy is bone marrow transplantation. [6] Correct and early diagnosis of LAD-1 is vital to the success of treatment and prevention of aggressive infections; earlydiagnostic suspicion and early treatment improve the prognosis.

Three different types of LADs are described in literature.[7] LAD-I, in which the beta 2-integrin family is deficient or defective. LAD II, in which the fucosylatedcarbohydrate ligands for selections are absent. LAD III is due to defective activation of all beta–integrins with tendency to bleed.[8] Pathogenically, LAD is characterized by loss of the leukocytes' ability to adhere to the endothelium during the inflammatory cascade, thus preventing their migration to the infected tissues.[9] Leukocyte adhesion defect, because of its rarity, presents a diagnostic dilemma. In this report, we described the findings of a patient with clinical features of LAD-I disorders patient. Our patient did not have any clinical findings at birth and was discharged at the status of the health infant and in his family none of his brother or sister has suffered from the same illness. Clinical presentation includes delayed separation of the umbilical cord for less than 1 month, leukocytosis, periodontitis recurrent infections of the skin, fever. LAD was suspected. Movahedi et al.[10] have described the clinical and laboratory findings of 15 patients with LAD I in Iran. The most commonly occurred manifestations were: recurrent infections (93.3%), poor wound healing (86%), oral ulcers (86%), and skin abscesses (80%)[10]. Patients with this disorder suffer from life-threatening bacterial infections, and in its severe form, death usually occurs in early childhood unless stem cell transplantation is performed. Bone marrow and other stem cell transplantation are the therapies of choice in leukocyte adhesion deficiency (LAD) and have a very high success rate. Thus, bone marrow or other stem cell reconstitution is a first-line treatment for severe leukocyte adhesion deficiency type I, in which less than 1% CD18 expression is detected. In addition, gene replacement therapy has shown good results in canine model of LAD 1 and may be beneficial also in human beings.[11,12]

KEY MESSAGES:

The possibility of leucocyte adhesion deficiency (LAD) should be kept in mind in the event of severe and recurrent infections in a child.

It is highly recommended that patients who diagnosed with mild to moderate LAD-I with recurrent skin infections and simultaneous weak responses to conventional therapy to undergo BMT to prohibit subsequent life-threatening complications.

CONCLUSION:

Pediatricians should keep LAD-1 in their mind; the rarity of this disease requires that physicians have a high index of suspicion in a child with history of delayed umbilical cord separation, repeated infections and marked leukocytosis with delayed unhealed lesions not improving well to medications even in the absence of infections.

ACKNOWLEDGEMENT:

We sincerely thank KFSH & RC staff for their valued contribution regarding the treatment of the patient and meanwhile providing us the useful data to create this study.

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Inverted Follicular Keratosis Scalp

Case Report

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ABSTRACT

Inverted follicular keratosis (IFK) is a solitary benign epithelial tumor of infundibular hair follicle, generally observed in middle-aged and older individuals. An elderly male presented with a rough & raised pink colored lesion on the bald area of parietal scalp since 4 months. Fine needle aspiration (FNA) followed by histopathologic examination of the lesion was done. The FNA smears revealed features suggestive of intra-epidermal inclusion cyst while the final diagnosis of IFK was established on histopathological examination. The present article describes a correlation between the cytopathological features and histomorphology of IFK. The cytopathological features of IFK have not been described in the literature yet, hence this article provides a chance to study cytopathological features of this rare lesion.

KEY WORDS: cytology, histopathology, inverted follicular keratosis (IFK), keratosis scalp

INTRODUCTION:

The inverted follicular keratosis is a rare benign tumor of the skin appendages. It was first reported by Helwig (1955) and was named as Inverted follicular keratosis[1] and also described its histopathological features. This benign tumor of the follicular infundibulum affects males twice as often as females. A common site of occurrence is face, especially the eyelids.[2] Other, common areas include cheeks and upper lip[3]. It may be mistaken for basal cell carcinoma or any other keratotic lesion. Typically these flesh-colored nodular or filiform lesions are between 0.3 to 1 cm in diameter. We describe the occurrence of this tumor on the scalp, which has not been reported so far. To the best of our knowledge, the cytopathological features of this rare lesion have been described for the first time by us.

CLINICAL HISTORY:

A 75-year-old male presented with a tiny, rough raised lesion on his scalp of four months duration on dated 24th May, 2010. He made an attempt to scrape it with his nail but was unable to remove it. Instead the lesion steadily increased in size. It did not respond to antibiotic therapy. At his initial consultation at the clinic, a pink flesh colored dome shaped nodule was found on the parietal region of the scalp, which measured 1.5 cm in its maximum diameter. The surface featured an irregular papule like appearance [Figure1(inset) magnified view]. The surgeon referred the patient to the cytopathologist for fine needle aspiration cytology (FNAC). Thereafter the lesion was completely excised under local anesthesia. The specimen was sent for histopathological examination.

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CASE REPORT:

Pathology examination:

On FNA, a tiny drop of thick creamy white material was obtained. Smears were prepared for cytological examination and stained by Papanicolaou and H:E stain. The smears were hyper-cellular comprising of thick sheets of enucleated hyper-keratinized squamous epithelial cells (Figure 2a). A few benign nucleated squamous epithelial cells and basaloid cells in tiny clumps were also seen (Figure 2b). No inflammatory reaction was present in any of the smears. Based on these cytological findings, it was

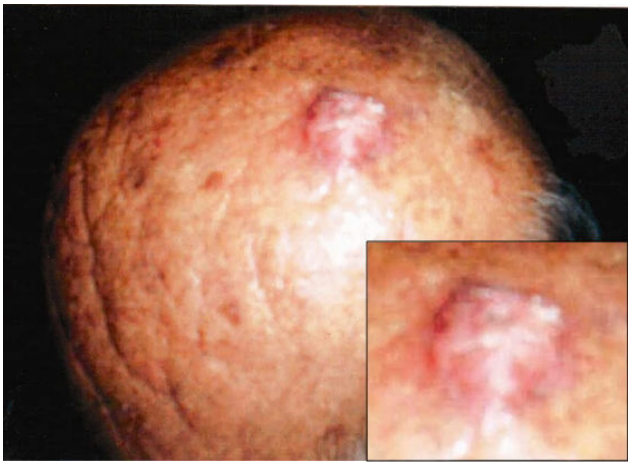

Figure 1: Clinical photograph with inset:Pink colored dome shaped nodule scalp with irregular margin.

the basaloid cells along the periphery. Some of the cell nests presented central keratohyaline material.

The cell nests of large eosinophilic, polygonal squamous epithelial cells 'Squamous eddies' were frequently seen (Fig.3c&d). There was no atypia of squamous epithelial cells. Basal cell layer was intact along each lobule. No mitotic figures were seen. There was sparse infiltration by chronic inflammatory cells at places along the lobules. No melanin containing cells were present in the tumor area. Normal sebaceous glands were also seen. Hence a histopathological diagnosis of IFK was given.

DISCUSSION:

IFK is a benign, usually solitary epithelial tumor originating from the hair follicle and presents as a flesh-colored nodule or papule. This filiform lesion arises from the follicular infundibulum and may be up to 1 cm in diameter.[3]

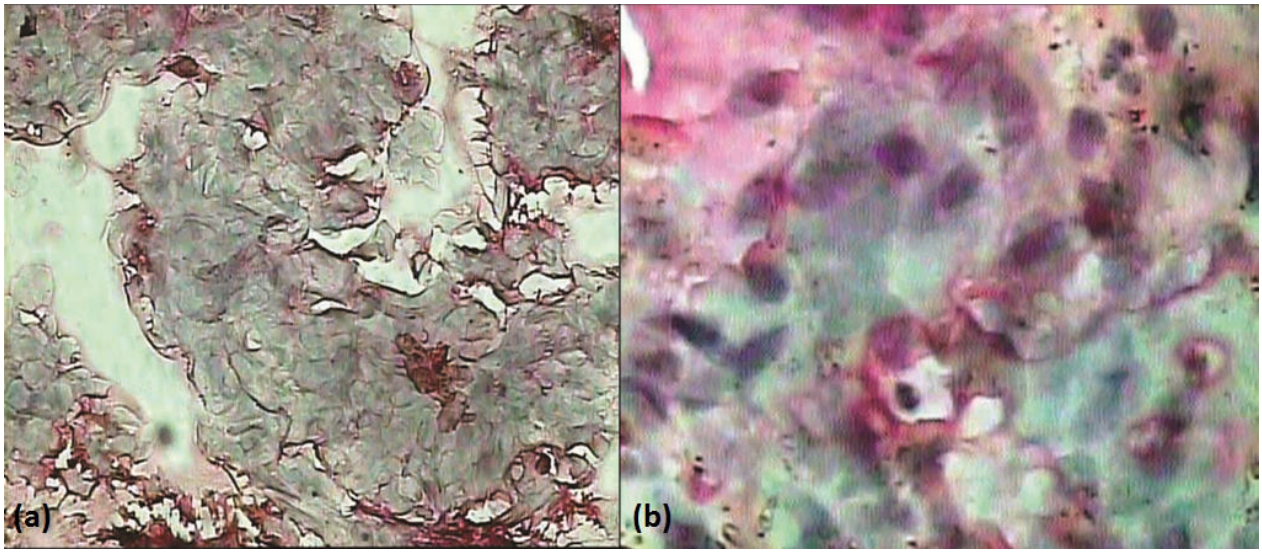

Figure 2: FNAC: (a) Smear showing irregular sheets of enucleated hyper-keratinized cells (Pap X 40) (b) Smear showing sheets of nucleated squamous epithelial cells and few basaloid cells (Pap X40).

The excised specimen was fixed in 10% neutral formal saline for paraffin sections which were stained by conventional H:E technique. Microscopic examination of the serial sections revealed that the biopsy piece was lined by intact epidermis. No evidence of papillary forms or exophytic growth on the surface of the lesion was seen (Figure 3a). There was an endophytic growth composed of proliferated squamous epithelial cells occupying the sub-epidermal zone. Multiple cell nests with parakeratotic and keratotic cells arranged in whorl like patterns, looking like cutaneous horn were present (Figure 3b). The cells were arranged in lobules which were lined by

IFK most often involves the parts of body with long-term sun exposure, such as head, neck, cheeks, upper lip and nose[1]. The upper eyelid being the most common site[2]. The solitary lesion in present case was situated on the parietal region of bald scalp, hence relatively more exposed to sun. The authors could not find any previous reference related to the occurrence of this lesion on the scalp.

FNA smears were richly cellular and

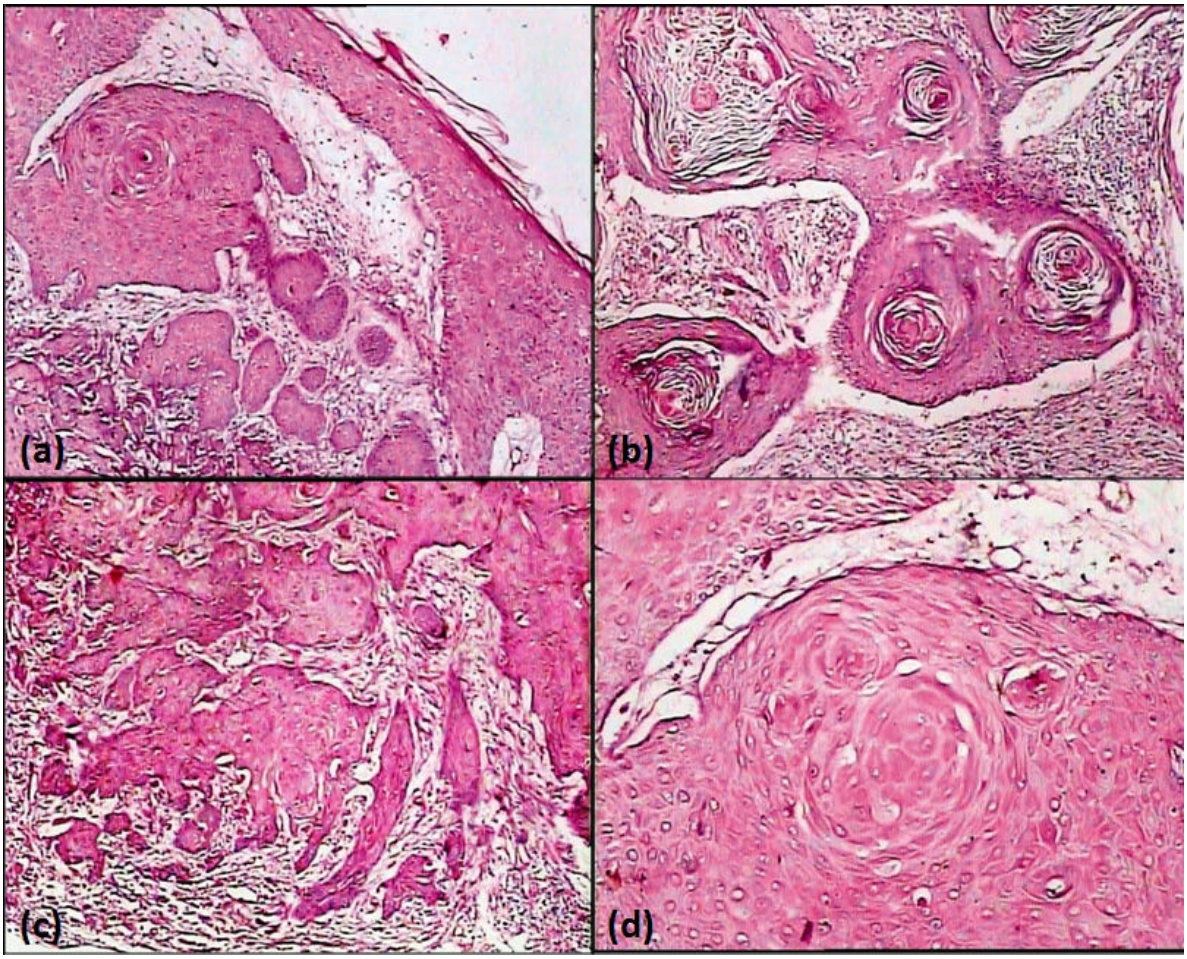

Figure 3: Histopathology :(a) Section showing endophytic growth composed of proliferated squamous epithelial cells arranged in lobules and parakeratotic and keratotic cells in whorl like patterns (H:E X 10). (b) Section showing tumor lobules and cell nests of large eosinophilic, polygonal squamous epithelial cells (horn cysts) (H:E X 10).(c) Section showing squamous cell eddies with keratohyaline material (H:E X40).(d) Squamous eddy in higher magnification (H:E X100).

contained sheets of mature keratinocytes and few basaloid cells. No inflammatory cells, necrotic debris or multinucleate giant cells were seen, as are being described in epidermal inclusion cysts. The number of basaloid cells was so scanty that possibility of trichoepithelioma could not be considered.

Histopathologically, four types of growth patterns have been identified: a papillomatous wart-like variant, a keratoacanthoma-like pattern, a solid nodular form, and rarely a cystic type.[4] The present lesion revealed typically an endophytic tumor with lobules or papillary projections, lined by basaloid cells and were extending into the dermis. Squamous eddies were characteristic i.e. they consisted of concentric layers of squamous cells in a whorled pattern with overlying variable parakeratosis and hyperkeratosis[5,6].

The numbers of keratotic horn cysts were comparatively more in the present lesion, probably because the lesion was situated on scalp. Hence the present case revealed a mixed pattern of tumor growth i.e. solid nodular type with keratoacanthoma like keratin horn cysts.

IFK is believed to be an inflammatory variant of seborrheic keratosis due to the presence of inflammatory reaction. However, this lesion was distinguished from seborrhoeic keratosis which usually contains horny invaginations, many of which are unrelated to hair follicles. Melanin pigmentation is often more prominent. But the most important distinction is the microanatomy: seborrhoeic keratosis is raised above the level of the surrounding skin, even when it is situated over a pressure point.[2] By contrast; inverted follicular keratosis has usually dominantly

always presents as a downward growing component.[4] IFK was distinguished from keratoacanthoma by absence of pale-staining squamous epithelium with overhanging edges. Instead, the presence of a lobular growth pattern with characteristic squamous eddies is hallmark of IFK.

The lesion also needs to be distinguished from squamous cell carcinoma.[2] Squamous carcinoma was excluded because of absence of epithelial atypia on serial sectioning and also the lobules had blunt edges. The nuclear and cytological pleomorphism of squamous carcinoma was also lacking and there was no evidence of infiltration. The squamous eddies have a monotonous uniformity that distinguishes them from epithelial pearls. Abnormal mitoses were not found in the lesion, and hence the doubt of it being a malignant lesion was excluded. Exclusion of possibility of malignancy was essential considering the age of the patient and duration of lesion with history of steady growth. Postoperative period has been uneventful. There is no evidence of recurrence even after five years of follow-up.

CONCLUSION:

Inverted follicular keratosis (IFK) is a benign tumor of hair follicle, observed in the middle aged and elderly individuals. The tumor involves the sun exposed areas mainly the head and neck region, the most common site being face. The present case was an elderly bald male with a slow growing painless lesion on the parietal region of the scalp. Fine Needle Aspiration was performed, the lesion was suspected to be keratotic type but final diagnosis of Inverted follicular keratosis was confirmed on histopathological examination. After excision, patient was followed up for 5 years. No recurrence was noted.

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Bilateral Anterior Fracture Dislocation of Shoulder

Case Report

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ABSTRACT

Anterior shoulder dislocation is a common orthopaedic shoulder injury. Bilateral dislocation is rare and usually posterior. Bilateral anterior shoulder dislocation with greater tuberosity fracture is a very rare injury. This report describes a case 23 years male who presented after a week of epileptic attack. It is concluded that a musculoskeleton survey should be done in every patient following epileptinc seizure.

KEY WORDS: fracture-dislocation shoulder epilepti C

INTRODUCTION:

Glenohumeral dislocation is most common dislocation and accounts for nearly 50% of all dislocations of body[1]. Of all Shoulder dislocations, 95% are anterior and 15% are associated with fracture of greater tuberosity[2]. Bilateral dislocation with fractures occur due to unusual muscular activity such as an electric shock or a seizures in epilepsy[3]. Incidence of simultaneous bilateral anterior gleno humeral fracture dislocation is extremely rare and is of traumatic origin[4&5]. Like other orthopaedics condition it can be easily missed if not suspected[6]. We discuss here one such case for mode of injury and the factor in delayed presentation.

CASE REPORT:

A 23 years old patient of epilepsy of 4 years duration without any antiepileptic medication presented to us with bilateral external rotation deformity of the shoulder and loss of normal contour of 7 days duration. This was followed after an epileptic attack when he had a fall from a height of 3-4 feet and landed on outstretched hands. Patient was then taken to a local hospital where he was given analgesics and antiepileptic drugs but his shoulder pain and deformity continued for which he was referred to our hospital.

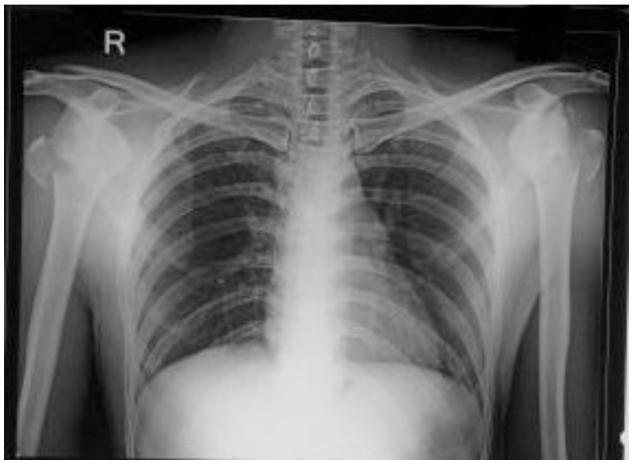

Figure 1: Pre-reduction X-Ray.

The physical examination of anterior shoulder dislocation is diagnostic3 and radiograph (AP view of both shoulders Figure 1) revealed bilateral anterior dislocation with Greater Tuberosity (GT) fracture. Both shoulder were reduced in emergency under general anesthesia by traction and direct pressure on the head of humerus. The post reduction x-rays showed GT displacement of more than 1 cm, necessitating fixation of GT[3] (Figure 2).

Screw fixation of GT was done by a lateral stab deltoid splitting incision under general

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anesthesia. Good fixation (Figure 3) was achieved and the limbs were kept in shoulder immobilizing sling for 10 days.

Physiotherapy was started and he gained full movement in 4 weeks time. He was cautioned for over head activities and advised to take regular neurophycisian checkup for antiepileptic medication.

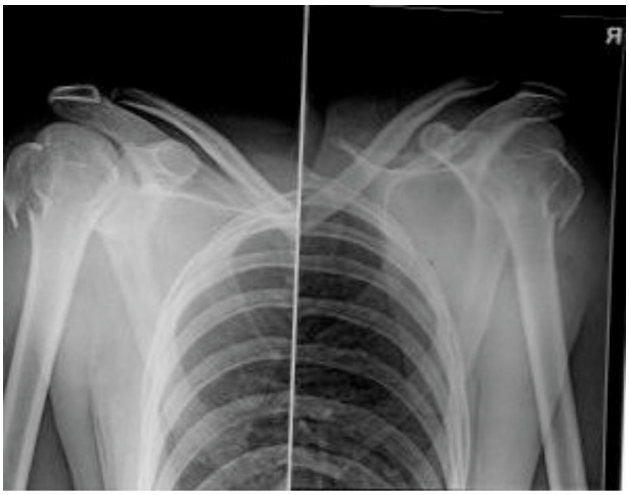

Figure 2: Pot Reduction X-Ray.

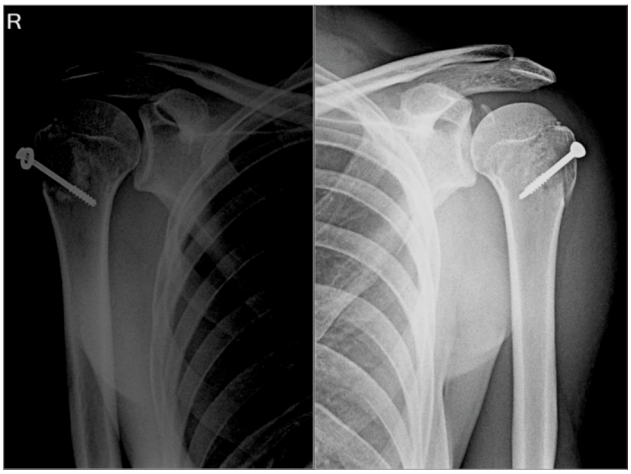

Figure 3: Post Operative X-Ray.

DISCUSSION:

The normal shoulder dislocates by direct trauma or fall on outstretched hand. The indirect force in abduction, extension and external rotation of shoulder results in anterior dislocation while axial loading of adducted and internally rotated arm produces posterior dislocation. Direct force in the form of blow on anterior side of the shoulder results in posterior dislocation.

Bilateral posterior shoulder dislocation occurs following unbalanced muscle contraction (in electric shock, epilepsy) i.e. Contraction of relatively weak external rotator and posterior fibres of deltoid are overcome by the more powerful internal rotators and succeeding adduction and internal rotation causes posterior dislocation[7].

Bilateral anterior dislocation was also noted following Convulsive disorder[6]. But the probable mechanism was not explained. Other authors explained bilateral anterior dislocation following seizure was not due to muscle contraction but on account of trauma by falling on floor after loss of consciousness following seizure[7].

In the present case, trauma following seizure resulted in Bilateral fracture dislocation. The delay in seeking treatment was on account of unawareness at the primary care centre. Incidence of GT fracture in shoulder dislocation is 15%. However the present case (bilateral dislocation, bilateral GT fracture) is a very rare entity.

Management of bilateral fracture dislocation shoulder is similar to unilateral[6]. In the present case closed reduction was followed by fixation of both the Greater Tuberosities, i.e. more than 10 mm displacement require surgical intervention[8] which resulted in good recovery of movements with proper physiotherapy and patient cooperation. The prognosis does not differ from unilateral case but it require aggressive physiotherapy programme for better outcome in these patient[9].

CONCLUSION:

In every patient following epileptic seizure, a proper musculo-skeleton survey should be done. Shoulder is a very vulnerable joint in epilepsy. In our opinion, awareness of this condition is of paramount importance for all the medical personnel who handle such cases. The relatives of the patient should also be made aware of this condition if pain, loss of movements or deformity continues at shoulder.

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Case Report

Unilateral Condylar Hypoplasia and Treatment Modalities

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ABSTRACT

Mandibular condylar aplasia or hypoplasia is an anomaly which usually manifests in association with various syndromes. When not seen in conjugation with any other development anomalies, it is an extremely rare condition. Only a few cases of Non Syndromic condylar aplasia or hypoplasia have been reported in literature till date . Proper diagnosis along with differentitation from syndromic cases is important as the treatment plan and prognosis varies. This report describes the surgical treatment done for a non syndromic condylar hypoplaia.

KEY WORDS: anomaly, condylar aplasia, facial asymmetry, hypoplasia

INTRODUCTION:

Facial abnormalities may appear as a result of many pathologic conditions, but there are two major categories of abnormalities: genetic or congenital and acquired. Mandibular condyle aplasia is a term used to describe total absence of the condyle. Earlier the term agenesis was used, but now being replaced by term aplasia i.e lack of development of tissue, as the condylar cartilage is considered a tissue rather than an organ[1,2]. Abnormality during the development and growth of TMJ may lead to condylar aplasia. These are associated with facial manifestation of syndromes such as Hemifacial microsomia, Treacher collins syndrome and Goldenhars syndromes[3].

In genetic or congenital, the early differentiation of tissues and or developmental processes are affected . Congenital hemifacial microsomia, Pierre Robin syndrome, Crouzon syndrome and cleft lip and palate.exemplify the genetic group. In the acquired variety, trauma or infection (suppurative otitis media) are belived to be the primary reasons for the anomally. Acquired condylar hypoplasia may develop after the loss of one or both condylar growth centres in very early stages of life and sometimes accompanied by ankylosis[2].

Condylar hypoplasia is defined as underdevelopment or defective formation of the mandibular condyle. According to Shafer et al congenital condylar hypoplasia of idiopathic in origin is characterized by unilateral or bilateral underdevelopment of the condyle, beginning early in life. In these cases condyle is generelly small (dysostosis otomandibularis). Condylar hypoplasia may be caused by local factor (trauma, infection, or middle ear infection) or systemic factors like bacteremia, rheumatoid arthritis and muccopolysaccharridosis[1,4].

We are presenting a rare case 'Non Syndromic condylar hypoplasia and its management'.

CASE REPORT:

A 27 year old patient reported to the department with the chief complaint of impaired facial aesthetics and chin deviation towards left side. The patient was in good general health and did not give history of auricular infection or trauma to craniofacial region. Family history was not suggestive of any such illness. History of presenting illness revealed that the deviation of chin to the left side of face first became apparent during early childhood and progressively

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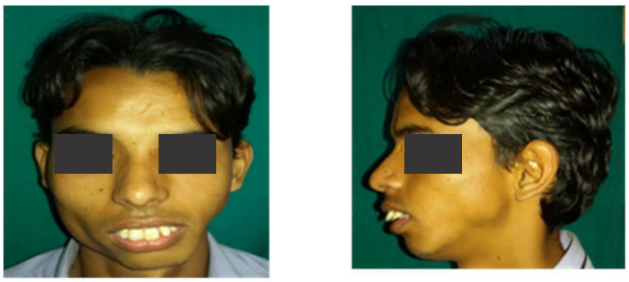


Figure 1: Preoperative Facial Profile.

worsened thereafter.

Clinically there was an obvious deviation of mandibular midline towards the left side of mandible in rest occlusion position. The range of mandibular movement was, however, normal.

EXTRAORAL EXAMINATION:

Clinically frontal view of face showed asymmetry at the lower third of face , flatting of the face on the right side with shifting of mandibular midline towards left by 12°. Left side condyle was not palpable. The rest of the face showed no abnormalities. There was no shortening of left body of mandible. There was no defect of auricle or pre auricular area and no facial nerve paresis paralysis. Opening of mouth was normal (interincisal distance 38mm).

INTRA ORAL EXAMINATION:

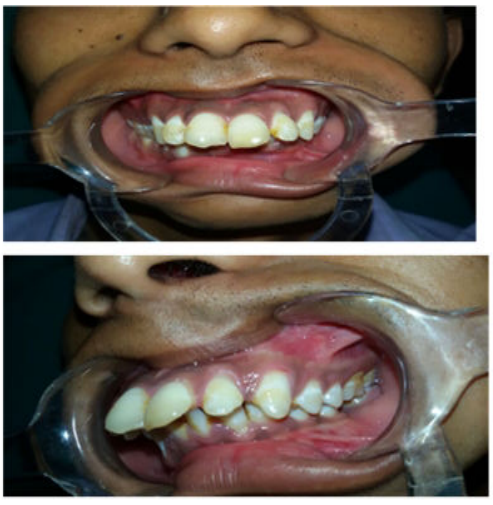
Intraoral examination showed left side shift of the midline by 12o . There was proclination of maxillary anterior teeth with 4 mm overjet and 5mm overbite. The occlusal plane was slightly tilted and there was no cross bite in upper and lower arch.

RADIOGRAPHIC FINDINGS:

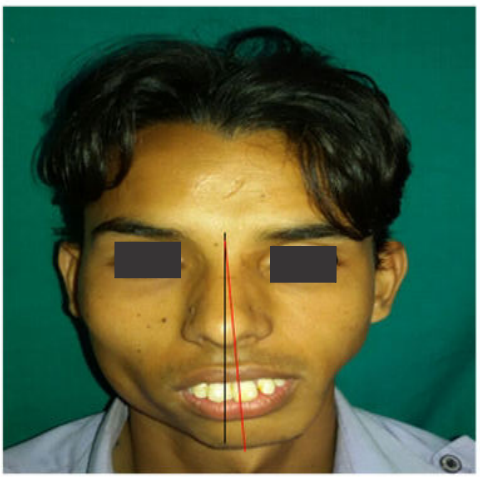
Panoramic radiograph with OPG and lateral cephalogram revealed missing normal condyle on the left side, shortening of condylar neck, ramus & body of mandible of the left side. There was marked antigonial notch on the left side. Significant proclination of maxillary anterior teeth with increased overjet and overbite was present. A missing first molar tooth on left side due to a past history of extraction. & Class II molar relationship was present on the left side; class I molar relation on the right side.

TREATMENT PLAN:

The patient refused pre surgical orthodontics due to financial constraints. A two step surgical intervention was planned for the patients in given circumstances. In first step anterior segmental osteotomy using Cupar's technique with down fracture, and 5 mm set back to correct anterior maxillary protrusion was executed. Camaouflage for facial asymmetry with a Medpore allograft in left body& angle of mandible was undertaken. In a second step lateral (towards right side) sliding genioplasty with advancement was done. The improvement in facial esthetics is very well appreciated in post surgical picture. The flattening seen on right side body of the mandible will require another Medpore graft to camouflage it.



CLASS I MOLAR AND CLASS I CANINE WITH OVERJET OF 4MM AND OVERBITE OF 5 MM.



LOWER MIDLINE SHIFTED TO LEFT SIDE BY 5MM AND 12° TOWARDS LEFT

Figure 2: Intraoral view and midline shift

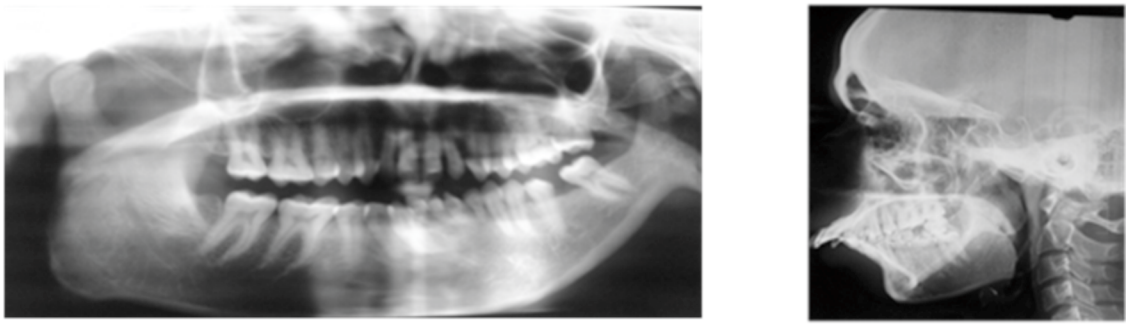


Figure 3: Pre-operative radiographs.

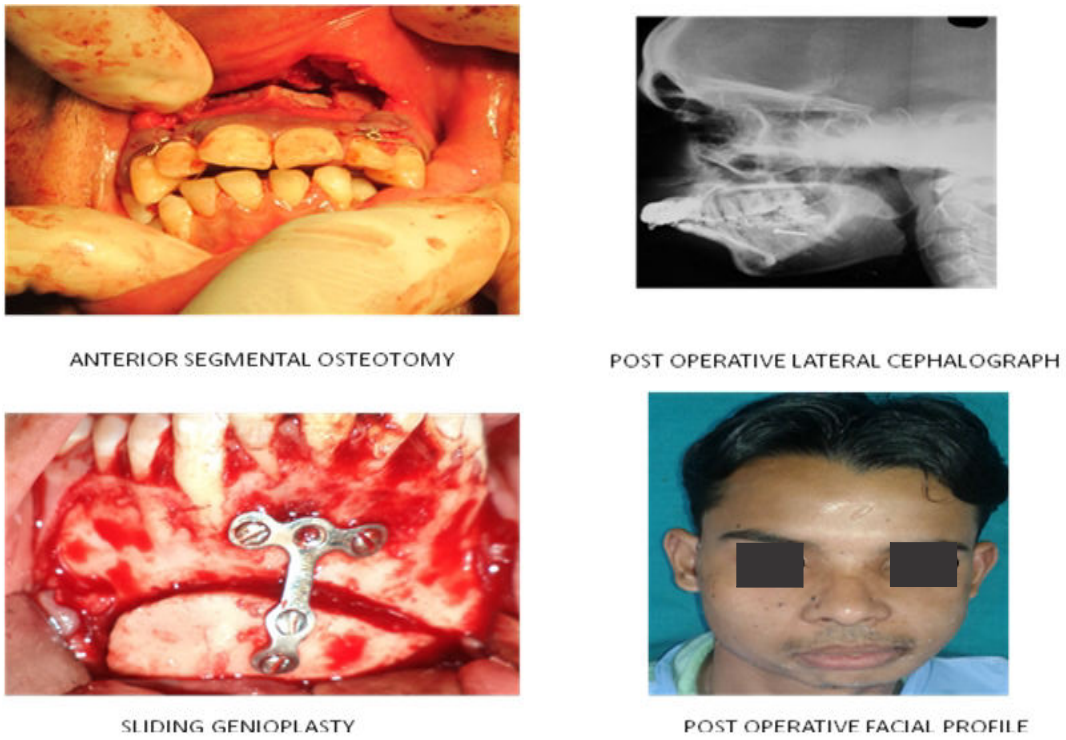


Figure 4: surgical and post surgical pictures.

DISCUSSION:

Treatment protocol for craniofacial microsomia vary widely. The clinical needs of patients with craniofacial microsomia depend entirely on the type and severity of the facial abnormalities, the aesthetic requirement of the patient and family and psychological support available to the patient[3].

Various treatment approaches have been proposed for treating condylar aplasia and hypoplasia. Most of the time it is treated by a multidisciplinary team comprising of an oral maxillofacial surgeon, plastic surgeon and orthodontist. [5]

Various surgical interventions can be planned depending on the severity of the asymmetry. The procedure undertaken for such corrections are vertical ramus osteotomy, Le Fort osteotomies to correct occlusal cant, distraction osteogenesis, variety of genioplastic procedures, cosmetic augmentation with bone grafts/allografts (camouflage surgery) and orthodontic correction of teeth[5,6].

A saggital split osteotomy is generally difficult to perfom on the deficient side of the mandible. In our case we did segmental maxillary osteotomy with Cupar's technique, a lateral sliding genioplasty and cosmetic augmentation with Medpore Allograft. No dental correction with orthodontic treatment was possible as patient refused treatment. The facial profile was dramatically changed and the patient was satisfied.

Patient is under follow up for another cosmetic correction for depressed mandible of right side and soft tissue correction with myotonic /myodynamic appliances.

CONCLUSION:

Patients with non syndromic condylar aplasiaor hypoplasia are a rare sub group in which the condition does not seem to be progressive. Integration of surgical and orthodontic treatment is required for good prognosis and predictable outcome. Also variety of surgical options give better results, but it depends entirely on the age at which the patient first reports.

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Pregnancy Associated Thrombotic Microangiopathy

Review Article

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ABSTRACT

The thrombotic microangiopathies (TMA) are a group of common microvascular occlusive disorders characterized by thrombocytopenia, microangiopathic hemolysis and multiorgan dysfunction. The pathological features are vascular damage manifested by arteriolar and capillary thrombosis with characteristic abnormalities in the endothelium and vessel wall. Pregnancy associated TMA is a life threatening rare disease reported to occur in approximately 1 in 25000 pregnancies, can occur at any stage of pregnancy and can be a key feature of several pregnancy related disorders such as thrombotic thrombocytopenic purpura (TTP) / Haemolytic uremic syndrome (HUS), congenital TTP(CTTP), HELLP syndrome, or acute fatty liver (AFL). The pathogenesis of inherited (Upshaw–Schulman syndrome) and idiopathic TTP is related to a deficiency of, or antibodies to, a metalloprotease that cleaves vWF and ADAMTS13, respectively. The role of complement factor H (CFH) dysregulation has been reported in cases of pregnancy related HUS. Therapy is specific for each disease entity ranging form plasma exchange (PEX) in TTP /HUS and termination of pregnancy or delivery in HELLP syndrome. The likelihood of survival in patient cases is as high as 80–90% with early diagnosis and aggressive treatment using PEX. The chance of missing the cases is high because of the rarity of these disorders and diagnostic dilemmas. The patients need comprehensive care in close conjunction with physicians and obstetricians. The purpose of this review is to provide a prospective of pregnancy associated TMA and management options available to reduce maternal morbidity and mortality.

KEY WORDS: HELLP syndrome, plasma exchange, postpartum, pregnancy, thrombotic microangiopathy

INTRODUCTION:

The thrombotic microangiopathies (TMA) are a group of common microvascular occlusive disorders characterized by thrombocytopenia, microangiopathic hemolysis and multiorgan dysfunction. These include hemolytic uremic syndrome (HUS), thrombotic thrombocytopenia purpura (TTP), and a third rare event, confined to puerperium , termed as postpartum renal failure.[1] TTP was first described in 1924 by Moschcowitz. It presents as a pentad of thrombocytopenia, hemolytic anemia, fever, neurological abnormalities and renal dysfunction in a 16 year old girl.[2] HUS which is characterized by acute renal failure, microangiopathic hemolytic anemia and thrombocytopenia, was first described in 1955 by Gasser et al. [3].Anemia is severe and microangiopathic in nature, with fragmented red blood cells (schistocytes) in the peripheral smear, high serum lactate dehydrogenase (LDH), circulating free hemoglobin, and reticulocytes.

TMA are diverse group of diseases which could be hereditary or acquired and occur in children and adults. Although diverse the TMA syndromes have defined uniting pathogenesis and clinical features of microangiopathic hemolytic anemia, thrombocytopenia, and organ injury.[4] The distinction between TTP and HUS is under debate. The pathogenesis in TTP is by von Willebrand factor (vWF) regulation by ADAMTS13 and in HUS is by alterations of complement activation and felicitates differential diagnosis.[5-8] A clinical distinction based on multi-organ involvement in TTP and renal involvement in HUS is not always apparent. Although many attempts have been made to differentiate TTP and HUS, none of the proposed criteria clearly separates the two syndromes. Even the most widely

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used criteria, the presence of neurological symptoms in TTP and of renal failure in HUS, fail to distinguish TTP from HUS since neurological involvement has been observed in HUS also. The fundamental pathological lesion, thrombotic microangiopathy, is identical in TTP and HUS, and identical aetiological agents and pathogenetic mechanisms have been proposed for both syndromes and thus the term TTP/HUS has been used to describe the patients of thrombotic microangiopathy representing a spectrum of single disease.[9, 10] The pathological features are vascular damage manifested by arteriolar and capillary thrombosis with characteristic abnormalities in the endothelium and vessel wall. Detachment of endothelial cells from the basement membrane due to vessel wall thickening and endothelial swelling with formation of platelet–fibrin hyaline microthrombi are histological features of TMA. The microthrombi occlude arterioles and capillaries.[11] In HUS/TTP the kidney shows characteristic vascular changes due to endothelial damage, that is, TMA, which should be clinically and morphologically differentiated from other diseases.[5] In a recent review the disorders have been classified as TMA syndromes based on available evidence describing a defined abnormality as hereditary or acquired with the cause and clinical features and initial management.[12] However, the disorders have also been described as in figure 1. Although rare pregnancy associated TMA is a serious disorder and has been reported in various stages of pregnancy and has led to significant maternal perinatal morbidity and mortality. Prompt diagnosis and treatment, distinction of this disease entity from other obstetric complications leading to diagnostic dilemmas are key issues laying emphasis in the need to understand the pregnancy associated TMA. This review is an attempt to describe the rare and important disease entity of pregnancy associated thrombotic microangiopathy and management options available to reduce maternal morbidity and mortality.

Pregnancy Associated Tma:

Pregnancy associated TMA is a life threatening rare disease entity reported to occur in approximately 1 in 25000 pregnancies.[13] Pregnancy is known to precipitate the disease both for the first time and also exacerbate the existing disease. During pregnancy, TTP usually presents in the second trimester [14] , whereas HUS usually occurs as a single episode, immediately after or some weeks after the delivery.[15] A study reported complication by thrombotic microangiopathy in 11 women with 13 pregnancies Between 1972 and 1997. Occurrence of disease before midpregnancy in 23%, in 62% peripartum and in 15% disease several weeks postpartum has been described[13]. In a review of the Oklahoma TTP-HUS registry of 335 patients no gender or race predilection has been found associated with pregnancy-associated TMA.[16] Another review has been published where 92 English-language publications from 1955 to 2006 of pregnancy-associated thrombotic thrombocytopenic purpura (TTP) in 166 pregnancies were analyzed. The review reported that initial and recurrent TTP presents most often in the second trimester (55.5%) after 1-2 days of signs/symptoms.[17]

Presenting Features of TMAs Associated with Pregnancy:

Thrombotic microangiopathy (TMA) can be a key feature of several pregnancy related disorders such as thrombotic thrombocytopenic purpura (TTP) / Haemolytic uremic syndrome (HUS), congenital TTP(CTTP), HELLP syndrome, or acute fatty liver (AFL). Most of the entities have overlapping presenting features . Typical differentiating features of common pregnancy-related TMAs, such as TTP , HUS pre-eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) are described in Table 1. British guidelines have been formulated in order to provide evidence based guidance for management of TTP and MAHA and clinical features have also been described. [18]

Acute renal failure is a serious medical complication during pregnancy and in postpartum period. HELLP syndrome is characterized by haemolysis, elevated liver enzymes, thrombocytopenia, and it is a severe form of preeclampsia. 10-20% of pregnant women with HELLP syndrome have severe form of preeclampsia/ eclampsia and the syndrome can occur in about 1-2/1000 pregnancies. Most cases (70%) occur before delivery between 28-36 weeks gestation. Rest of the 30% cases usually occur within 48 hours post delivery. A case of a 25-year-old woman, at 34 weeks of pregnancy with significant hepatic dysfunction, with deterioration of the renal function, and development of severe coagulopathy has been reported . She had episodes of abdominal pain, urine frequency with feature of urinary tract infection and proteinuria. Diagnosis of AFL of pregnancy was suspected. Liver biopsy was not feasible because of poor clotting, whereas abdominal ultrasound showed no steatosis. Initially she got only supportive therapy, but because of

deterioration of her condition she was treated with plasma, platelets and erythrocyte transfusions, leading to correction of the clotting problems.[19] Postpartum HUS following abruption placenta has been also reported in a 32 year old woman. Persistent renal failure, microangiopathic hemolytic anemia characterized by fragmented red cells, thrombocytopenia and histopathologic findings of the renal biopsy, supported the diagnosis of HUS.[20] Another case has been reported, eight days post delivery, where patient had severe vomiting followed by hematuria, spontaneous bruising, marked pallor, icteric sclera, and lethargy. The 23-year-old parturient had laboratory findings of hemolytic anemia, thrombocytopenia, and acute renal failure. The patient died after a day of onset of symptoms and the diagnosis was confirmed only post-mortem examination.[21] Post partum TTP/HUS has been reported in three patients, referred to a tertiary care center, presenting with thrombocytopenia, microangiopathic hemolytic anaemia with or without fever and severe renal failure .[22]

Pathogenesis and Diagnosis of Pregnancy Associated TMA:

Pregnancy is associated with increasing concentrations of procoagulant factors, decreasing fibrinolytic activity of von Willebrand factor cleaving metalloproteinase .[23] Prompt diagnosis on basis of clinical examination, laboratory investigations and clinical cause of the illness and early treatment intervention has led to better prognosis in management of life threatening pregnancy associated TMAs. Evidence has been generated in involvement of ADAMTS13, the regulator of von Willebrand factor in pathogenesis of pregnancy-associated microangiopathy. A series of 15 pregnancies with congenital deficiency of ADAMTS13 activity known as Upshaw-Schulman Syndrome has been reported. [24] The pathogenesis of inherited (Upshaw–Schulman syndrome) and idiopathic TTP is related to a deficiency of, or antibodies to, a metalloprotease that cleaves vWF and ADAMTS13, respectively. This defect alone, however, is not sufficient to result in TTP as individuals with a congenital absence of ADAMTS13 develop TTP only episodically. Additional provocative factors have not been defined. An antibody to ADAMTS 13 is found in many but not all sporadic cases of adult TTP/ HUS. Recent genetic and molecular studies have shed more light on the pathogenesis of thrombotic microangiopathy in atypical HUS, that is, disturbances of various aspects of the complement system.[5] Preeclampsia, HELLP syndrome, HUS/TTP, AFL are multiple displays of pregnancy associated TMA and it is important to correctly identify each in early stages so as to manage the disease.[25] Preeclampsia results in TMA as it is hypertension-related disease during pregnancy as a result of systemic small artery spasm , damage and activation of endothelial cells, platelet activation and microthrombi formation.[26] HELLP syndrome is also clinically difficult to differentiate from TTP/HUS as it is characterized by hemolysis, elevated liver enzymes and thrombocytopenia. During late pregnancy AFL is a severe complication associated with coagulation dysfunction with acute presentation with gastrointestinal symptoms.[27] Postpartum haemorrhage is one of the presenting features complicating pregnancy. Low haemoglobin, hematocrit , high lactic dehydrogenase levels and poor urine output with vaginal bleeding may confuse the clinician to diagnose wrongly. The peripheral smears of patients developing thrombocytopenia post delivery could help in early diagnosis and recognition .[20]

Pentalogy of fever, TTP, microangiopathic hemolytic anemia, central nervous system damage, and kidney damage is hall mark of TTP. Under the shear stress of blood flow , adhesion of platelets and thrombosis occurs due to reduced enzymatic activity of ADAMTS13 which promotes excessive synthesis of the super-large polymer of vWF.[28,29] The discovery that the major regulatory protein complement factor H (CFH) has role to play in the pathogenesis of postpartum HUS has been a landmark development [30] . The damage to blood vessel has been implicated due to deficiency of CFH level resulting in continuous activation of complement bypass. In a retrospective analysis assessment of incidence of complement dysregulation in patients presenting with pregnancy associated HUS in a French cohort of adult patients with TMA was done. Complement abnormalities were detected in 18 of the 21 patients and the need for better understanding of complement deregulation in pregnancy with identification of high risk cases for close monitoring and also for developing anti complement targeted agents in the treatment of these disorders. Suspicion of the disease in absence of other identifiable causes , full blood count, peripheral blood smear, lactate dehydrogenase, reticulocytes, clotting, fibrinogen, urea and electrolyte, Troponin I/Troponin T, calcium , pregnancy test, blood group with antibody screen, ADAMTS13, Hepatitis A/B/C, HIV serology , autoantibody screen , amylase, Direct Coombs test , Liver function tests are the investigations to be performed before initiating treatment. Pre-treatment

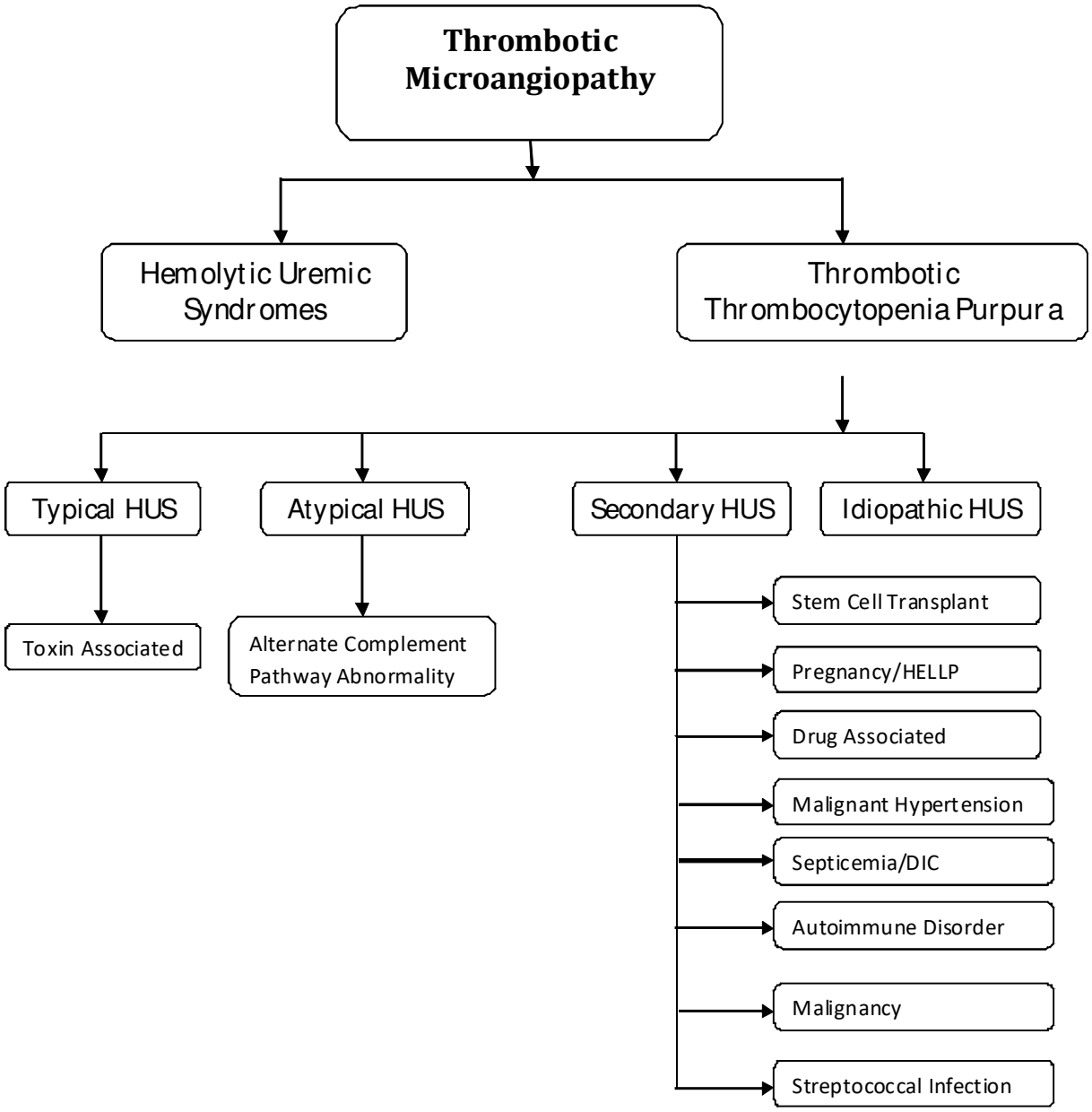

Figure1: Thrombotic Microangiopathies: TTP and HUS.

ADAMTS13 assays are useful to distinguish congenital from acquired TTP and other pregnancy associated TMAs. Early diagnosis and prompt treatment are important for better prognosis. Urine analysis, stool tests and CT scan brain, chest /abdomen / Other investigations can be delayed after treatment has been started.[18] A summary of various studies and review articles suggesting pathogenesis, diagnosis and management of TMA are shown in Table 2a and Table 2 b.

Treatment Options and Prognosis:

The definitive treatment of pregnancy associated TMA is delivery but is not related to remission. Guidelines have been developed by American Society for apheresis, on the use of therapeutic apheresis in clinical practice on basis of evidence generated and the treatment of TMA is based on the categories I to IV and grading recommendations from 1 A to C and 2A to 2 C.[31] If a thrombotic

Table.1 Differentiating features in pregnancy associated microangiopathies .

	TTP	HUS	HELLP	AFLP	PET
Peripheral Smear (MAHA)	++	+	+	±	+
Coagulopathy	–	–	+	++++	±
Thrombocytopenia	+++	++	++	+	+
Renal Involvement	++	+++	±	++	±
Neurological involvement	+++	±	±	+	++
Liver involvement	±	±	+++	+++	±
Hypertension	±	++	+	+	+++

PET, pre-eclampsia; HELLP, haemolysis, elevated liver enzymes and low platelets; TTP, thrombotic thrombocytopenia purpura; HUS, haemolyticuraemic syndrome; AFLP: acute fatty liver of pregnancy; MAHA, microangiopathic haemolytic anaemia.

microangiopathy (TMA) cannot be fully explained by a non-TTP pregnancy-related TMA, then the diagnosis of TTP must be considered and Plasma exchange (PEX) has been recommended to be started (2B). Evidence has been generated that PEX therapy can help continuation of pregnancy and successful delivery when TTP has been diagnosed in first trimester. Regular ADAMTS13 supplementation has been recommended for mothers with congenital TTP throughout pregnancy and the post-partum period (1A). Close liaison with an obstetrician with a special interest in feto-maternal medicine is required in mothers with TTP (1A). In mothers with acquired TTP, ADAMTS13 activity should be monitored throughout pregnancy to help predict the need for adjuvant therapy and outcome (1B). A comprehensive approach including hemodialysis, antihypertensive treatment, anticoagulation medications, antibiotics, water electrolyte correction, and immune inhibition along with PEX is key to success in the management of TTP/HUS. Earlier the administration of comprehensive treatment better is the prognosis . Plasma exchange helps to remove harmful materials in the plasma. In certain conditions transfusion of fresh frozen plasma can complement the deficiency of platelet aggregation inhibitory factors and relieve the disease.[25] Pre-conceptual counseling is advised for subsequent pregnancies and women of child bearing age should be counseled about potential risks of pregnancy and combined oral contraceptive pill (COCP) (2B).[18] With aggressive treatment using PEX likelihood of survival in cases of postpartum hemolytic uraemic syndrome (HUS) is as high as 80-90% as compared to only 10 % in patients not treated with PEX. Patients of postpartum HUS presenting with thrombocytopenia, microangiopathic hemolytic anaemia with or without fever and severe renal failure have been reported to have been managed aggressively with PEX in conjunction with hemodialysis with normal renal function tests, increased platelet counts and decreased lactic dehydrogenase levels. Awareness amongst treating physicians, early diagnosis and treatment with PEX have been recommended as the key factors in reducing maternal mortality due to postpartum HUS especially in developing countries .[22] Postpartum HUS following abruption placenta treated with PEX therapy led to recovery of a patient from thrombocytopenia and renal failure. High degree of suspicion to recognize thrombotic microangiopathy in pregnancy with aggressive therapy is recommended.[20] PEX is a successful treatment modality in early pregnancy and continuation of pregnancy can be done . However in late pregnancy the effort is for successful delivery in conjunction with PEX. Plasma infusions should be done if the facility for PEX is not instantly available and then patient be referred for PEX especially in resource constraint countries.[32,33,34] PEX therapy thus should be initiated on suspicion of TMA in pregnancy and continued till the end of delivery and even postpartum.[35] A case of postpartum HUS has been reported where early diagnosis and prompt treatment was done. The option of PEX is still underutilized and such cases under reported due to lack of awareness of diagnosis amongst obstetricians

Table 2(a): List of various studies showing pathogenesis, diagnosis and treatment of thrombotic microangiopathies.

SN	Author/ Year	Objective	Results	Conclusion
1	Mokrzycki MH, et al, 1995[33].	The case report describes rare syndrome of Thrombotic thrombocytopenic purpura (TTP) which presenting with thrombocytopenia, microangio-pathic hemolytic anemia, central nervous system symptoms, fever, and renal abnormalities.	This case report describes the earliest presentation of TTP in pregnancy (6 weeks of gestation) we could identify in the literature treated successfully with a prolonged course of plasma exchange.	The diagnosis of TTP in pregnancy bore a poor prognosis and high fetal mortality in early gestation. This study reviewed the differential diagnosis and pathogenesis of TTP and therapeutic options for better prognosis by plasma exchange with description of the case.
2	Dasche, et al, 1998 [13].	To characterize perinatal outcomes and long-term maternal complications from thrombotic microangiopathy manifested during pregnancy, and to review the clinical course and long-term follow-up of pregnant women with this condition over past 25 years.	The study revealed an incidence of one per 25,000 births amongst pregnancies complicated by thrombotic microangiopathy . In ten other pregnancies, disease developed either peripartum (62%) or several weeks postpartum (15%). In three pregnancies (23%), severe and refractory disease developed before mid-pregnancy. The response to treatment was generally prompt. However, disease recurred at least once in 50% of these, two during a subsequent pregnancy and long term sequela occurred.	Thrombotic microangiopathy complicating pregnancy is rare, and with careful evaluation, it should not be confused with atypical preeclampsia. With prompt and aggressive treatment including plasma exchange, the likelihood of immediate survival is high; however, long-term morbidity and mortality are common.
3	Mannucci PM, et al, 2001 [23]	In patients with thrombotic thrombocytopenic purpura (TTP) formation of intravascular platelet thrombi has been linked to congenital or immunomediated deficiencies of the metalloprotease that cleaves physiologically von Willebrand factor (vWF) reduce or abolish the degradation of ultralarge vWF multimers. The study evaluated the specificity of low protease plasma levels in the diagnosis of TTP.	The protease was measured in 177 control subjects of different ages, in 26 full-term newborns, and in 69 women during normal pregnancy, using an enzyme immunoassay, The spectrum of acute phase reactions and multiorgan involvement was also studied Pathologic conditions were also investigated included decompensated liver cirrhosis (n□=□42), chronic uremia (n□=□63), acute inflammatory states (n□=□15), and the preoperative and postoperative states (n□=□24). In healthy individuals protease levels were lower in persons older than 65 than in younger persons and in new borns, and in the last 2 trimesters of pregnancy than in the first. Protease levels were also low in patients with cirrhosis, uremia, and acute inflammation, and they fell in the postoperative period. There was an inverse relation between low protease and high plasma levels of vWF antigen and collagen-binding activity.	The fact that the protease is also low in several physiological and pathologic conditions indicates that low plasma levels of the vWF cleaving protease are not a specific beacon of TTP.
4	Wu VC, et al, 2002 [22].	To describe a case of postpartum hemolytic uremic syndrome (HUS), an unusual complication that presents with microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure after delivery.	A 32-year-old patient (gravida 3, para 1, artificial abortion 1) developed postpartum HUS following abruptio placenta. After cesarean delivery due to abruptio placenta, the patient developed acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia followed by hypertension. The patient recovered and showed recovery from thrombocytopenia Plasma exchange led to and improvement in renal function.	It is important to observe peripheral blood smears in patients with abruption placenta with thrombocytopenia post delivery and initiate management.
5	Zheng XL, et al, 2004 [38]	The study aimed to prospectively analyze ADAMTS13 activity and inhibitor levels in 37 adults with TTP. Therapeutic plasma exchange is an effective empiric treatment for thrombotic thrombocytopenic purpura (TTP), but how therapy affects the level of a disintegrin and metalloprotease with thrombospondin type 1 motif 13 (ADAMTS13) or inhibitor has not been reported in many patients.	In 16 of 20 patients with idiopathic TTP ADAMTS13 level at presentation was lower than 5% and none of 17 patients with TTP associated with hematopoietic stem cell transplantation, cancer, drugs, or pregnancy the level was lower (p<.00001). Out of the 16 patients with lower ADAMTS13 activity Seven (approximately 44%) had inhibitors. Plasma exchange led to complete clinical remission and a rise in ADAMTS13 level in 8 patients followed serially with ADAMTS13	Though a rare disease with poor outcomes with prompt diagnosis and treatment, lives could be saved with good outcomes clinically in patients diagnosed of Post-partum HUS as shown by the described case.

			activity lower than 5% but no inhibitor at presentation. Neither a rise in ADAMTS13 activity nor a reduction in the inhibitor titer was seen in 4 patients with low ADAMTS13 activity but high-titer inhibitor (> 5 units/mL) , 3 had recurrent disease and 1 died. 10 out of 17 patients with AD-AMTS13 activity higher than 25%, died. Mortality rate for idiopathic TTP was 15%, whereas mortality for nonidiopathic TTP was 59% (p <.02).	
6	Iannuzi M, et al , 2006 [26].	To describe a case of a 37-year-old woman admitted after twin delivery by caesarean section and severe renal failure.	Diagnosis of hemolytic-uremic syndrome, on basis of anuria, anemia, and moderate thrombocytopenia was made. Consecutive sessions of plasma exchange, substitution with fresh frozen plasma, hydrocortisone and ACE inhibitors were the treatment modalities. Recovery was evident with disappearance of active haemolysis and improvement of renal function within fifteen days. A genetic study demonstrated the absence of HF1 and MCP mutations.	Though a rare disease with poor outcomes with prompt diagnosis and treatment, lives could be saved with good outcomes clinically in patients diagnosed of Post-partum HUS as shown by the described case.
7	Martin JN, et al, 2008. [17]	A study / review of 92 publications of pregnancy-associated thrombotic thrombocytopenic purpura (TTP) in 166 pregnancies from 1955 to 2006.	2-4 times higher aspartate aminotransferase (AST) values and lower total lactate dehydrogenase (LDH) to AST ratios (LDH to AST ratio = 13:1) are exhibited in TTP with preeclampsia (n= 28) compared with TTP without preeclampsia (LDH to AST ratio = 29:1). Initial and recurrent TTP presents most often in the second trimester (55.5%) after 1-2 days of signs/symptoms. Maternal mortality is higher with initial TTP (26% vs 10.7%), especially with concurrent preeclampsia (44.4% vs 21.8%, p < .02).	For improved care and diagnosis of TTP and HELLP syndrome/ preeclampsia rapid and readily available laboratory testing is needed. Even when plasma therapy has improved maternal mortality initial TTP confounded by preeclampsia/hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome remains a significant maternal-perinatal threat.
8	Shrivastava M, et al , 2009 [22].	The study evaluated response of treatment of patients, diagnosed as postpartum HUS presenting with thrombocytopenia, microangiopathic hemolytic anaemia with or without fever and severe renal failure to our managed aggressively with PE in conjunction with hemodialysis.	All patients showed clinical improvement, along with laboratory indicators like normal renal function tests, increased platelet counts and decreased lactic dehydrogenase levels.	Awareness amongst treating physicians, early diagnosis and treatment with PE could be the key factors in reducing maternal mortality due to postpartum HUS in developing countries. The likelihood of survival in cases of postpartum hemolytic uraemic syndrome (HUS) is as high as 80-90% with early diagnosis and aggressive treatment using plasma exchange (PE)
9	Fujimura Y, et al, 2009[24]	A study of Upshaw-Schulman syndrome (USS) a congenital thrombotic thrombocytopenic purpura (TTP) due to mutations in the gene that encodes for ADAMTS13 and clinical correlation.	Nine women from six families of 37 patients with USS (24 females, 13 males) belonging to 32 families were included. Out of the nine patients, six had thrombocytopenia misdiagnosed as idiopathic thrombocytopenic purpura during childhood. Thrombocytopenia occurred during the second-third trimesters in each of their 15 pregnancies, with 16 babies (one twin pregnancy), often followed by TTP. All nine patients included had severely deficient ADAMTS13 activity.	Measuring ADAMTS13 activity in the evaluation of thrombocytopenia during childhood and pregnancy is of importance.
10	Dekker R R, et al , 2011[27].	A retrospective study to assess maternal death (between 1983 to 2006) and severe maternal morbidity (between 2004 and 2006) from acute fatty liver of pregnancy (AFLP) in the Netherlands.	0.13 MMR per 100,000 live births (95% CI 0.05-0.29) and maternal morbidity 3.2 per 100,000 deliveries (95% CI 1.8-5.7) from AFLP were reported.	Severe maternal morbidity and in some cases mortality are outcomes of AFLP a rare condition and treatment be initiated once diagnosed or patients should be referred to a tertiary care hospital for treatment.

10	Dekker R R, et al , 2011[27].	A retrospective study to assess maternal death (between 1983 to 2006) and severe maternal morbidity (between 2004 and 2006) from acute fatty liver of pregnancy (AFLP) in the Netherlands.	0.13 MMR per 100,000 live births (95% CI 0.05-0.29) and maternal morbidity 3.2 per 100,000 deliveries (95% CI 1.8-5.7) from AFLP were reported.	Severe maternal morbidity and in some cases mortality are outcomes of AFLP a rare condition and treatment be initiated once diagnosed or patients should be referred to a tertiary care hospital for treatment.
11	Delmas Y, et al , 2013[39].	To report a case of atypical haemolytic-uraemic syndrome (aHUS) a disease of uncontrolled complement alternative pathway activation	A week after childbirth 26 year old woman was admitted for aHUS. A 26-year-old woman was admitted 1 week after her first childbirth for aHUS with creatinine 6.2 mg/dL (550 µmol/L), haemoglobin 3.6 g/dL (36 g/L), lactate dehydrogenase 2155 U/L (upper normal limit 248), 9% schizocytes and platelet count 49 × 103/µL (49 × 109/L). Daily PE was started with 60 mL/kg fresh frozen plasma substitution. On Day 3 post-admission owing to family history and suspected genetic background the patient was switched to, 900 mg eculizumab.	Eculizumab is an effective therapeutic option in aHUS which induces terminal complement blockade (TCB), and has been approved by the US Food and Drug Administration and the European Commission.
12	Mu J, et al, 2015[21].	To report a rare case of unexpected death due Postpartum hemolytic uremic syndrome (PHUS), a severe thrombotic microangiopathy (TMA) that is clinically characterized by hemolytic anemia, renal dysfunction, and low platelet levels after childbirth.	After an uneventful pregnancy and delivery by cesarean section a 23-year-old developed severe nausea and vomiting followed by hematuria, spontaneous bruising, marked pallor, icteric sclera, and lethargy. After 29h of onset of symptoms the patient died. The patient had hemolytic anemia, thrombocytopenia, and acute renal failure. PHUS was confirmed on postmortem examination.	Early diagnosis and awareness about disease entity amongst obstetricians is of importance PHUS. Renal biopsy is suggested as histopathological finding of endothelial cell injury in renal micro vessels is characteristic feature of PHUS and speed and accuracy of diagnosis are crucial to optimize maternal outcomes.

and initiation of prompt treatment.[36]

A study demonstrated importance of prenatal management , differential diagnosis of pregnancy associated TMAs , acquired and congenital TTP . Prophylactic plasma infusions, aspirin and low molecular weight heparin have been effective in congenital TTP and unlike pregnancy associated TTP/HUS, PEX is not necessary therapy.[37] Corticosteroids have to be administered carefully preferably only in cases with severe ADAMTS13 deficiency. Monoclonal anti-CD20 antibody, rituximab has emerged as a promising new therapeutic approach in patients with severe refractory idiopathic TTP. Contrary to TTP where pregnancy can be continued with patients on regular PEX therapy, termination of pregnancy is the only treatment option in HELLP syndrome. Platelet Transfusions are contraindicated in TTP /HUS while in HELLP , preeclampsia the platelet transfusions can be given to achieve the desirable preoperative counts . However a sudden rise in platelet counts warrants thrombosis exacerbating the disease and low dose aspirin is indicated in such cases .[19]

ADAMTS 13 activity and inhibitor levels can help monitor the disease in terms of outcome and treatment tailoring in TTP patients. In a prospective study a mortality rate of 15% for idiopathic TTP and 59% for non idiopathic TTP was reported along with good predictive value of these assays. [38] Eculizumab treatment through induction of terminal complement blockade has been used along with daily PEX therapy with success in post partum atypical HUS.[39]

CONCLUSION:

The thrombotic microangiopathies (TMA) are a group of common microvascular occlusive disorders and pregnancy associated TMAs such TTP, HUS , HELLP syndrome, or AFL are life threatening serious conditions presenting with diagnostic difficulties and treatment dilemmas leading to high maternal mortality and morbidity . Though rare, the spectrum of disorders has different etiopathogensis and requires immediate treatment on case to case basis and based on the diagnosis, the therapy is different for different disease entity. With awareness about the disease amongst treating midwives, physicians and obstetricians, high index of suspicion, early recognition and aggressive therapy with PEX, plasma infusion and termination of pregnancy or successful

Table 2(b): List of review articles showing pathogenesis, diagnosis and treatment of thrombotic microangiopathies.

SN	Author/year	Observation	Conclusion
1.	Ruggenenti et al, 2001 [6].	To review the disease pathogenesis clinical symptoms and outcomes of HUS and TTP.	Depending on whether renal or brain lesions prevail, both are pathologically indistinguishable however, clinically different entities. TMA is associated with injury to endothelial cell, loss of physiological thrombo resistance, leukocyte adhesion to damaged endothelium, complement consumption, abnormal von Willebrand factor release and fragmentation, and increased vascular shear stress. Shiga toxin-associated HUS reveals good outcomes in childhood, whereas, atypical and familial form HUS and TTP end up with renal and neurological complications.
2.	Fakhouri F, 2007 [8].	To review the advancement in identification of disease symptoms of HUS, TTP, TMA and to identify research gap.	The new advances in the identification of pathogenic features-- deficiency of the metalloprotease ADAMTSl3 in TTP and association of mutated complement proteins with atypical HUS has helped the clinicians to distinguish between the two diseases. The research gap was identified as questions needed to be answered: is it important to patient management that HUS be distinguished from TTP? By discussing what is known about the pathogenesis, clinical features and treatment of these two conditions we address this question, and propose a new nomenclature for TMA.
3	Desch K 2007 [11].	To review the recent progress and shared pathophysiologic mechanisms of HUS and TTP.	Both the disorders were considered to be same disease processes possessing distinct clinical and pathologic entities.
4	Benz K et al, 2009 [5].	To review the epidemiolocal pathogenesis and typical morphological aspects of morphological aspects of all the three types of membranoproliferative glomerulonephritis (MPGN), HUS and TTP is on light microscopical, immunohistological or immunofluorescence and electron microscopical level.	Dysregulation of the complement system, distinct molecular defects in C3 factor H, the major regulatory protein of the alternative pathway of complement activation and deficiency of von Willebrand factor (VWF)- cleaving protease i.e. ADAMTS13 were highlighted.
5	James N. George, 2014	To review the knowledge of disease pathogenesis, management, and outcomes of primary TMA syndromes that has accelerated in recent years.	The recent advancement in understanding of primary TMA has enhanced the diagnosis and management of the and have created opportunities for specific treatments thereby reducing the mortality and also answering previously unrecognized long term morbidities.

delivery, depending upon pregnancy associated TMA, can reduce mortality and morbidity in pregnant women to a great extent.

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Is a Tomato better than an Apple?

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ABSTRACT

"An apple a day, keeps the doctor away." This 17th Century idiom has always caused a lot of interest in medical researchers. With the help of modern day technology and advances in the field of medicine, it is now possible to find if it is really true or its time for a rethink the adage.

KEY WORDS: nutritive value, apple, tomato

Short Communication

The Apple:

Malus sylvestris. In Hindi, known as *'Seb'*, the apple is one of the most popular fruits in the world. The Bible begins with man and woman eating it. It took an apple to help Newton discover some basic laws of gravity. However, from a nutrtitive stand point, the apple does not compare favourably with the other fruits that are popular in India, especially with reference to the cost. Apple has practically no Vitamin-A or Vitamin-C. It has very small amounts of mineral nutrients. Their iron content is just 0.1*mg* per 100*g*. Though it contains fair amounts of calcium and phosphorus, other fruits which are cheaper and easily available *(sitaphal, sapota and banana)* contain more of these mineral salts.[1] Apple is a fair source of fibre or roughage. Roughage in diet is said to protect a person from disorders of the alimentary canal. Perhaps the phrase "An Apple a day keeps the doctor away" is more true for people from Western Countries where the diet contains very little roughage because of consumption of processed foods. A recent study published by American Medical Association concludes that,"Evidence does not support that an apple a day keeps the doctor away; however, it is a health habit."[2] When the apple pieces are exposed to air, certain chemical substances such as tannins in the fruit causes some other nutrients to react with atmospheric oxygen resulting in browning and the destruction of vital nutrients. Browning can be avoided by placing the pieces in a salt solution.

Table 1: Comparison of Nutritive Values (*per*100*gm*) source: Nutritive Value of Indian Foods, National Institute of Nutrition.

Nutritive Value	Macronutrients	Apple	Tomato
Calories (*kcal*)		52	18
Carbohydrate (*g*)		13.8	3.9
Protein (*g*)		0.3	0.9
	Vitamins		
Vit - A (*IU*)		54	833
Vit - C (*mg*)		4.6	13.7
Vit - E (*mg*)		0.18	0.54
Vit - K (*g*)		2.2	7.9
Folate (*g*)		3	15
	Minerals		
Calcium (*mg*)		6	10
Iron (*mg*)		0.12	0.27
Magnesium (*mg*)		5	7
Phosphorus (*mg*)		11	24
Sodium (*mg*)		1	5
Potassium (*mg*)		107	237

The Tomato:

Solanum lycopersicum. Tomato is regarded as the most popular 'vegetable- fruit'. India is the second largest producer of tomatoes with about 17,500,000 metric tonnes produced annually. Tomato is a rich source of Vitamins, particularly Vitamin-C,

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potassium, folic acid, and carotenoids, such as lycopene. Normal food processing does not adversely affect it nutritive value making it nutritionally desirable.

It it commonly believed that tomato consumption may result in the formation of bladder stones and in-suitable for those to who suffer from gout or uric acid diseases. However, analysis of tomato show that the vegetable- fruit contains around 4mg of oxalic acid per 100g of fruit. Infact, tomatoes contain less purines than carrots, potatoes, cabbage and other vegetables and less oxalic acid than beets, potatoes, cucumbers and lettuce. Purines & oxalic acid are substances that are generally known to be associated with bladder stone formation. Adequate amount of water intake is advised in those who have a tendency for bladder stone formation.

Recent studies highlights the relationship between consuming tomato and its products with reduced risk of various conditions like obesity, cardiovascular disorders, and cancer and improve high cholesterol levels.[3-5]

Since tomato is a fruit of good nutritive value, especially with regards to vitamins and is easily available at a relatively low cost; its inclusion into everyday diet of young, growing children as well as adults should be encouraged.

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